ANNALS
OF THE
RHEUMATIC DISEASES

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The Official Journal
of the
EMPIRE RHEUMATISM COUNCIL

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VOL. I. : NO. 4
OCTOBER, 1939

LONDON
H. K. LEWIS & Co. Ltd.
Six Shillings net
Annual Subscription, One Guinea, post free

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RHEUMATIC DISEASES

THE OFFICIAL JOURNAL OF
THE EMPIRE RHEUMATISM COUNCIL

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Vol. I., No. 4. OCTOBER, 1939

LONDON
H. K. LEWIS & Co. Ltd.

This Journal is the continuation of the "Reports on Chronic Rheumatic Diseases" hitherto published by authority of the British Committee on Chronic Rheumatic Diseases of the Royal College of Physicians. That Committee has transferred responsibility for the publication to the Scientific Advisory Committee of the Empire Rheumatism Council.

Owing to the Declaration of War, it is possible that the publication of "The Annals" may be interrupted for a period. (It was decided to proceed with the printing of this number as it was practically ready for publication on September 2nd.) Subscribers whose payments have covered future numbers may be confident that, in cases of interruption, their interests will be safeguarded.

Printing of an index to this, the first volume, has been postponed until publication of the next number.

MADE AND PRINTED IN GREAT BRITAIN

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ANNALS
OF THE
RHEUMATIC DISEASES

THE TREATMENT OF THE RHEUMATIC DISEASES IN THE UNITED STATES AND THE CONTINENT OF EUROPE

By W. S. TEGNER

Preface

The Empire Rheumatism Council in March, 1938, selected me for the Sir Alexander Walker Travelling Scholarship to study the measures taken for the treatment of the rheumatic diseases in the principal foreign centres. Sir Alexander Walker, whose generous gift provided the means for this tour of investigation, had expressed as his intention a desire to provide for workers in British rheumatism clinics, existing and about to be established, information gathered by direct observation as to the methods employed in Europe and America in the war on rheumatism. He believed that this would give some useful guidance in planning for Great Britain a national scheme of treatment. This, having had the cordial approval of the Scientific Advisory Committee and the Research Advisory Committee of the Empire Rheumatism Council, I took as my "general instruction"; and, sensible of the honour of being chosen for so important a task, have sought to give effect to it to the best of my ability.

Leaving London in May, I travelled to Holland, Denmark, Sweden, Germany, France, Italy, Roumania, Czecho-Slovakia, Canada, the United States in that order (Appendix I. gives a detailed itinerary), and returned to England in March, 1939. The report of my observations is now presented.

The idea that it would be useful to begin with a survey of methods of treatment at present in general use in Great Britain, after careful consideration, was rejected. Such a survey, to be comprehensive, would have had to be very lengthy, and it would have covered mostly familiar ground. But, where necessary, in reporting on foreign systems, I have referred to British

ideas and practice on the particular matters dealt with. This seemed the best course to follow for the convenience of practitioners (and of members of the lay public interested in the problems of rheumatic disease); in a busy world it is desirable to come as promptly as possible to the marrow of the matter.

To report on methods of treatment I recognised as the task. I found, however, that it was essential, because of the quite indivisible association between systems of treatment and the ætiological facts, or surmises, on which they are founded, to give some attention to that side of the matter. There has not been attempted—could not, within the limits of this report, have been attempted—a complete conspectus of European and American opinion on the problems of ætiology. But to record the ætiological views held by different eminent workers in the field of rheumatic disease whom I had the advantage of meeting—views on which they largely base their systems of treatment—will be, I am confident, useful. The fact that these vary, sometimes to an extreme degree, illustrates the complexity of the task which medical science faces in bringing under control the rheumatic diseases. That wide variance of views is not a prompting for discouragement. In time, ætiological uncertainties should be solved by perseverance in research; and, meanwhile, treatments having their origin in theories which are as yet not proven may be wisely given clinical trials. From such trials, if carefully controlled and recorded, there may come approaches to proof.

To some extent international disturbances hampered the work of investigation in Europe; indeed, at one stage circumstances threatened to become perilous. Only a small part of the planned tour, however, had to be abandoned. I was greatly aided by many letters of introduction kindly given to me. The Foreign Office, at the instance of Lord Horder, secured the assistance of His Majesty's representatives in the countries visited, assistance which was of inestimable value in places overcast by war clouds. Dr. W. S. C. Copeman, the Hon. Medical Secretary of the Council, was able to put me in close personal touch with his friends in several centres. Dr. Van Breemen, Secretary of the International League against Rheumatism, was most kindly helpful in Europe, and Dr. Philip Hench of the Mayo Clinic in the United States. To these, and to many others, I express my sincere thanks.

To the Empire Rheumatism Council I leave the duty of expressing gratitude to Sir Alexander Walker for conceiving the idea of, and granting the means to put into effect, this voyage of exploration. Apart from what value its "log" may prove to have (on which it is not for me to express an opinion), I learned from many quarters that our scientific colleagues abroad were impressed by the evidence that Great Britain was now embarking upon a strenuous effort to take a full part in the world war on rheumatism, and that in doing this recognised the great value of keeping in close touch with foreign work on the subject.

I.—Observations on Ætiology

In Europe and America, as in Great Britain, there may be noted a strongly increasing interest in the ætiological factors of rheumatic disease. Research workers are growing in numbers and intensity of application to particular problems. If I may venture a generalisation which is perhaps, with many exceptions, correct, European workers are toiling through the maze with somewhat more positive confidence that they have the right key than their colleagues in Great Britain. One hears more often the phrase "I am sure" than "I think."

To record in the first place observations regarding that most vexatious of this group of diseases—rheumatoid arthritis.* Until recently ætiological research has generally sought to incriminate the streptococcus as its cause. Because of the prevalence of streptococci in the upper respiratory tract, in the bowel, and in other foci of infection among patients suffering from rheumatoid arthritis, most bacteriological work has been directed towards this group of organisms, though lately in several quarters there has been (as the result of many disappointments in obtaining a definite verdict against this accused) a tendency to search for a virus source of infection.

In America, Cecil, Stainsby and Nicholls, working at the New York Hospital with a very elaborate technique, have been able to grow the hæmolytic streptococcus from the blood of patients suffering from rheumatoid arthritis, and have decided that this organism is the causative factor. But this verdict has not been generally accepted. Dawson and his group, working

* Throughout I follow the nomenclature agreed by the R.C.P. Committee on Rheumatism.

at the Presbyterian Hospital (New York), were unable to confirm the findings. They observed that the blood serum of about 70 per cent. of their rheumatoid patients agglutinated the hæmolytic streptococcus. Yet in 30 per cent. of cases of unquestionable rheumatoid arthritis the blood serum did not agglutinate this streptococcus. They concluded, therefore, that it is not a specific reaction in this disease. They consider, however, that it is of some diagnostic value, and use it as such.

Rosenow, at the Mayo Clinic, is able to grow an "arthrotropic" strain of non-hæmolytic streptococci from the upper respiratory tract of his arthritic patients, and he considers this the causative organism. Burbank (New York) has observed mutation of organisms causative of rheumatic conditions, and therefore is able to correlate the work of those who indict hæmolytic or non-hæmolytic streptococci or staphylococci. His observations are not generally accepted.

Other workers, such as Jarlov (Copenhagen), find that they can produce arthritis in experimental animals by injections of streptococci. But many do not agree that this arthritis is the same disease as human rheumatoid arthritis.

Lowenstein is able to isolate an attenuated form of the *Bacillus tuberculosis* from almost all cases of rheumatoid arthritis, and such observers as Secher (Copenhagen) and Francis Hall (Boston) find these experiments difficult to contradict. There are others who hold that tuberculosis plays some part in the production of rheumatoid arthritis, but these are in the minority. From European centres I gathered no observations of special interest on the points referred to above—viz., as regards the possible relation of streptococci, hæmolytic or non-hæmolytic, or other organisms to rheumatoid arthritis.

In the matter of the importance of septic foci as agencies in causing rheumatoid arthritis I chronicle a very wide divergence of views among American and European authorities. Many research workers in America ascribe a large part in the ætiology of rheumatoid arthritis to the "septic focus." But I noted that Cecil (New York Hospital), once a firm believer in this theory, has recently modified his views. Graham (Toronto) reports that an investigation which had been made in that city into dental infection occurring in diabetes mellitus, gastro-intestinal disease and rheumatoid arthritis showed an equal incidence in all three

diseases. Other workers observe that a "suitable soil" is necessary for infection to lead to the development of the disease, and that this accounts for the fact that only a very small minority of patients with infected teeth or tonsils develop rheumatoid arthritis. Fletcher (Toronto) suggests that patients do not become suitable soil for the development of rheumatoid arthritis until one or two generations of their ancestors have been chronically under-nourished and thus have "prepared the soil."

On the other hand, in Germany a very high degree of importance is attached to the septic foci as the causative factors; sometimes to the exclusion of all other factors. It was very interesting to note the development of this theory—and the consequent system of treatment—at Aachen. There, Slauck, Gehlen and their entire group agree that all chronic rheumatic diseases can be associated with the presence of such septic foci. They hold that toxins from the focus, whether it be in the teeth, tonsils, appendix or genital tract, may attack joints or tissues directly or, in the case of rheumatoid arthritis, through the nervous system. They explain that these toxins attack the autonomic ganglia and the anterior horn cells of the spinal cord, and that thus we get muscular wasting, muscular fibrillation and capillary spasm, the last accounting for the pallor and œdema of the affected joints. Slauck claims to be able to demonstrate muscular fibrillation in the small muscles of the foot in all cases of rheumatoid arthritis, and that it is, in fact, a type of chronic anterior poliomyelitis. They claim at Aachen that treatment depends firstly on the discovery and removal of a septic focus. If the removal of one discovered focus does not cure, there should be search for, and eradication of, further foci which *must* exist if the condition continues to progress. Following the extirpation of all septic foci, repair of the peripheral circulatory defects should be sought by physiotherapy.

Throughout Germany the septic focus and its treatment are prominent in the minds of rheumatism workers, and I noted how often chronic appendicitis was diagnosed as the causative factor.

As to the part that endocrines play in the production of rheumatoid arthritis, American opinion is divided. Whether there is such an entity as "menopausal arthritis" seems, in the opinion of the majority of workers, doubtful. Bauer and his group record that 16 per cent. of the women in their series developed

rheumatoid arthritis within three years before or after the menopause, but they show that this is the percentage of women in the general population within the same age group. They observe, however, that there is a definite increase in the incidence of the disease during the decade following the menopause. Summarising the majority of opinion of American students, it is that there is no proof that endocrines play a primary part in the production of arthritis.

On this point Sundelin (Sweden) observes that there is much secondary glandular dysfunction after rheumatoid arthritis has developed.

Observations made by Hench (Mayo Clinic) are of great interest in the ætiological study of rheumatoid arthritis. He drew attention to the fact that the existence of jaundice may exert in certain cases a beneficial effect on rheumatoid arthritis. He has noticed and reported also the beneficial effect of pregnancy. This observation was also pointed out to me by Touw (Leyden).

Hench has also noted that operation under anæsthesia often brings about an improvement in the general condition of his rheumatic patients (an observation which all cannot confirm). He is seeking some common factor in these three phenomena that may "activate a relief mechanism," and speculates whether the liver cannot be the connecting link between them; that possibly there may be a hyperhepatosis that needs correcting or a hypohepatosis that needs stimulating. In this connection it is interesting to note that Boots (New York) has observed a similarity in the cyanotic palms of patients with rheumatoid arthritis and of patients with cirrhosis of the liver, and he questions whether the liver is not involved in both conditions. Regarding this, one must consider the French concept of "hépatisme" in relation to rheumatic disease.

Observations on psychological factors in the development of rheumatoid arthritis are being carried out extensively in the United States. At the Hospital for Chronic Diseases (New York), research has been undertaken by psychologists into the part played by such factors. They claim that this part is a very large one. These observations, perhaps, may be taken as bringing us back to the consideration of "promotive factors" preparing

the soil for the onset of rheumatic disease, including in such factors worry and other mental strain, as well as faulty physical régime and predisposition arising from hereditary causes.

Such "promotive factors," perhaps, had better be separated from consideration of ætiological factors. Strictly speaking, they are hardly "causes," rather conditions which are favourable for causes to operate. Therefore they would come more appropriately in the province of treatment. Medical practice in dealing with a morbid state in a patient usually has to study not only the attacking infection, if that can be determined, but the general conditions which may be assisting the attack.

To turn now to ætiological factors of rheumatic fever. In this disease, as in rheumatoid arthritis, there is a strong and growing tendency among research workers to regard the case against the streptococcus as non-proven, and to turn their attention to a virus as the possible causative factor.

Danielopolu (Roumania) told me that he regarded rheumatic fever as resulting from an infection with a specific virus. This virus, he holds, may attack by itself or, as commonly happens, have the portals of entry opened and the subject's resistance weakened by a previous streptococcal infection.

In America most observers are now studying the natural history of the disease, and collecting a vast amount of data about its incidence. The work of Duckett Jones (House of the Good Samaritan, Boston) impressed me as important. In this hospital a series of 1,700 cases of rheumatic fever have now been studied. All the work done has not been able definitely to inculpate the streptococcus, and attention has now been directed to a virus. A year ago Duckett Jones and his colleagues isolated a virus from the heart tissue and pericardial fluid of a post-mortem subject who had died with active rheumatic fever. This virus regularly produced in mice an infection with pulmonary and cardiac changes; but this infection they do not yet claim to be the same as human rheumatic fever. Ferrets and swine are susceptible to the virus, but it dies out in passage through ferrets, and can thus be distinguished from the influenza virus, which increases in strength in passage through ferrets. They observe that neutralising antibodies in the serum of rheumatic fever convalescents will protect mice against up to 1,000 lethal doses of the virus. They thus conclude that they have a virus prob-

ably related to rheumatic fever. Duckett Jones does not think that this virus is connected with the elementary bodies found by Schlesinger and Signy.

The relationship between rheumatic fever and rheumatoid arthritis remains a doubtful question. Many English observers regard them as separate entities. But in Germany and in rheumatism centres of Scandinavia they are regarded as having a common ætiology, and the development of rheumatoid arthritis from rheumatic fever is regarded as not unusual. I was told at the *Forschungsinstitut für Rheumabekampfung* (Berlin): "The textbook manifestations of acute rheumatic fever are now comparatively rarely seen, for the manifestations of arthritic infections are swinging from the acute to the chronic in the course of the evolution of the disease."

Dawson (New York) holds very definitely that there is a connection between the two diseases, and thinks they may be the differing response of individuals to the same ætiological factor. Other workers do not observe this connection, taking the view that whilst one does find an occasional case of rheumatoid arthritis with rheumatic carditis, and also occasionally a case acute enough to be regarded as rheumatic fever, but which develops into rheumatoid arthritis, such cases are not commonly regarded as representing a significant percentage in the total incidence of rheumatic disease.

Curiously, little work on the pathology of rheumatoid arthritis is being done in Europe. In America considerable work has been done, but there I found wide disagreement. Dawson and his group (New York) hold that the nodules of rheumatic fever and rheumatoid arthritis are fundamentally of the same pathological structure. Bauer and Bennett (Boston) find the two types of nodule by no means easy to differentiate histologically, and think that there is nothing specific in the histological structure of joint tissue in rheumatoid arthritis. On the other hand, Hench and Ghormley (Mayo Clinic) observe that the histological structure of the joint tissue in rheumatoid arthritis is quite definitely specific.

* * *

To record now some observations on the rheumatic disease which in our nomenclature is styled fibrositis. In Great Britain

we accept and consider ourselves familiar with the condition which we term fibrositis, and it is generally accepted in Europe. But in America I found among some observers what was to me at first a surprising scepticism as to its existence at all. Dawson states that he has not seen the condition. Bauer acknowledges that there is a syndrome which the English term fibrositis, but observes that there is little evidence that fibrous tissue itself is primarily affected. He suggests that much more investigation is needed on this subject, and that perhaps muscle and muscle proteins which undergo certain chemical change produce this syndrome. Hench and Slocumb (Mayo Clinic) accept the English concept of fibrositis and have done much work on it. They feel strongly, however, that English workers are apt to accept far too complacently Stockman's work without confirmation. Their observation of the condition is at present directed to establishing its pathology by biopsy and autopsy.

* * *

The relation between gout and rheumatism all know to be a matter of some controversy. In Europe I found "gouty arthritis" widely recognised as an entity, and gout considered as one of the factors in the ætiology of chronic polyarthritis. In Berlin "gouty arthritis" was diagnosed with certainty in cases where the blood uric acid was over 4 mgm. per cent. At Aix-les-Bains they are firm believers in arthritis of a mixed type, of infective nature, yet associated with a high blood uric acid and a gouty tendency. In America, however, many workers observe that "they never see gout," and that it is purely a European disease. Yet that gout does extensively exist in America has been amply proved by Hench. His observations on the provocation of attacks of acute gout by surgical operations, and by the administration of certain drugs such as salyrgan, may prove of value in the prevention of such attacks. Galantha's pathological work (Mayo Clinic) on the morbid anatomy of gout and her technique for the staining of uric acid crystals in histological sections has done much to show how urate deposits are laid down in this condition. No American observer that I met is able to accept gout as playing a partly causative rôle in rheumatoid arthritis, nor to agree with the European concept of chronic gouty arthritis independent of attacks of acute true gout.

* * *

Osteo-arthritis is generally regarded in Great Britain as a degenerative change in joints following wear and tear and trauma. Some observers, however, consider it to be a true manifestation of infection. Thus Burbank (New York) and his group not only accept it as such, but claim to be able to reproduce it bacteriologically in laboratory animals. Many observers are not content that our knowledge of the ætiology of osteo-arthritis is sufficient. With Hench I was able to examine a woman of 101 who had spent a life of hard work on farms and whose joints most certainly have been exposed to considerable wear and tear, and she had no vestige of senescent or degenerative arthritis.

Of considerable interest in regard to the actual development of the joint lesions in osteo-arthritis have been Phemister's (Chicago) observations on bone necrosis in caisson disease. This is a very rare manifestation of the disease in which massive necrosis takes place in the spongiosa and ends of the long bones; there follows considerable regeneration from the corticalis and a condition of osteo-arthritis results. These observations have led Phemister to surmise whether this is not due to fat or nitrogen embolism in the internal arterioles of the bone, and whether osteo-arthritis may not develop from such an interruption to the blood supply.

* * *

The connection between psoriasis and rheumatoid arthritis has led to much speculation. Hench believes that there is an entity, "psoriatic arthritis," which can be distinguished from rheumatoid arthritis. He bases his belief on the observations: (*a*) that where the diseases co-exist, the exacerbations and remissions of joint and skin diseases are associated; (*b*) that there is a close anatomical relationship between psoriasis of the finger-nails and the arthritis of the terminal interphalangeal joints; and (*c*) a parallelism in the response to therapy of the two conditions. Neither Dawson nor Bauer (in whose series 2·7 per cent. of patients showed psoriasis as well as arthritis) can accept such a clear-cut line between psoriatic arthritis and rheumatoid arthritis.

Similarly, and basing his conclusions on similar observations, Hench claims that the arthritis sometimes associated with ulcerative colitis can be differentiated from rheumatoid arthritis, and is, in fact, a separate condition. Fletcher (Toronto) finds

that about 50 per cent. of patients suffering from ulcerative colitis have suffered at some time from arthritic manifestations. But again the majority of observers only go so far as to note that in some way patients suffering from ulcerative colitis are more prone to rheumatoid arthritis.

* * *

In view of the present interest taken in a possible virus causing rheumatoid arthritis, Dawson's observations on the arthritis caused by the virus of lymphogranuloma venerea seem particularly significant. He has shown conclusively that among the coloured population of the United States there is a type of arthritis always associated with a lymphogranuloma infection and a positive Frei test. This arthritis is characterised by painful swelling starting in the larger joints and spreading to the smaller. It is indolent and resistant to treatment, but never leads to joint destruction as seen radiologically. It has been confused until recently with gonococcal or with rheumatoid arthritis, but Dawson's work seems definitely to have established its independence. It is only likely to occur as an extreme rarity in Great Britain.

* * *

Of interest, too, in the clarification of the problem of joint diseases is the syndrome being observed at the Mayo Clinic which they term angio-neuro-para-arthrosis. This is a condition first described by Solis Cohen (Chicago), and one which Hench and Slocumb regard as a true entity. It may occur in any age or sex, and is characterised by recurrent painful swellings around or near the joints, but with no true endo-arthritis. The attacks of swelling last for two or three days, occurring at intervals of days or of years. Attacks may be associated with fever and elevation of the sedimentation rate, but this is not constant. As the signs may disappear as quickly as they appear, prolonged observation of the patient is necessary to establish the existence of the condition. Hench and Slocumb consider that they have been able to differentiate the condition from gout and rheumatic fever.

These observations on ætiology—whether put forward as conclusions or as theories—coming as they do from workers whose views demand serious consideration, impress the fact of

how much uncertainty has yet to be cleared up on the subject of the causative factors of rheumatic disease. They lead to a sympathetic understanding—though not necessarily acceptance—of de Pap's statement that the main ætiological problem is whether we can ascribe rheumatoid arthritis to any single cause or whether it is the result of many coincident causes; and Pemberton's view that rheumatoid arthritis is not a single disease, but the result of a combination of diseases.

II.—Methods of Treatment Abroad (General Régime; Drug, Endocrine, Vaccine, Physical and Other Therapy)

Medical science knows no barriers of national boundaries, and aspires to make available to all the world whatever any individual may discover of value to relieve human suffering, so there are no closely guarded secrets to be sought out by an explorer. Any who claim to have "secrets" come under suspicion. Nevertheless, exchange of knowledge by correspondence can never reach the ideal of perfection, and it is therefore recognised as a valuable part of professional education to take opportunities to study at first hand theories and practice in foreign centres. Such direct investigation can give information hardly attainable by a study of written records, because in many cases a method can be effectively studied only in the laboratory or the clinical ward of the worker who has evolved it, and who can personally explain the basis on which it is founded, and the exact technique which should be followed in its practice.

From the very valuable opportunity given to me to devote almost a full year to investigate methods of treatment of the rheumatic diseases in Europe and America I certainly gained much knowledge, and I shall endeavour to chronicle it in the most convenient form, first making reports under various headings, and then seeking in a "discussion" to record what seem to me points of special interest for British treatment centres.

It is conventional, when giving an account of systems of medical treatment, to deal first with general measures and then to proceed to the particular. Although, by following that convention in this survey, certain points of major interest may not be brought to the immediate forefront, it will be probably best not to depart from it.

General Treatment.—There is more agreement on the general methods of caring for the rheumatic patient than on the particular, although even regarding the latter there is some divergence of opinion. Still, a large measure of agreement exists; and it suggests that, despite the regrettable deficiency in exact knowledge of the ætiology of the rheumatic diseases, the medical practitioners of different countries have at their disposal means of treatment which can cure a large proportion of cases, and give much alleviation in still larger proportion.

There is almost universal concurrence that the sufferer from rheumatism and the person judged to be predisposed to rheumatism need a special degree of precaution from physical, bacterial, chemical or psychological trauma than the normal individual. This leads, in plans of treatment, to advice in regard to diet, clothing, housing conditions, climate, etc., on which, as before noted, there is a wide measure of agreement, but on some points differences of opinion which will be noted in due course.

In the matter of diet, the result of my investigations in Europe and America led to the general conclusion that less importance was attached to what may be termed "specialised" diets than is the case by some workers in Great Britain. On this point I must note, however, that it was not within the scope of my inquiries to visit any of the numerous special dietary clinics dealing with all classes of ailments, but only treatment centres specially devoted to rheumatic disease. Most of the medical staffs of these are coming to the conclusion that an optimum diet with a full quotient of accessory food factors is necessary for the rheumatic patient. The changing fashions of high or low protein diet, which had had their day, were coming to be considered as fanciful, and the general consensus of opinion was in the direction of seeking the optimum diet for the individual patient, not a system of diet applicable to classes of rheumatic sufferers.

Much work has been done (and continues) on vitamin metabolism in the rheumatic diseases, but the general impression was that the lowering of such vitamin metabolism was secondary to the general condition, and not causative. There is thus agreement that the rheumatic patient needs a generally wholesome mixed diet in accordance with his capacity of assimilation.

The question of climate in its relation to the incidence of rheumatism, if it is studied from the observations of workers in

different countries, remains very open. It is the general impression in Great Britain that cold and damp conditions, clay soils and seaside localities are all potentially unsuitable.

There appears to be as much rheumatism on the granite hills of Sweden as on the flat islands of Denmark and Holland. It is the custom of Scandinavian countries to place their sanatoria for the treatment of rheumatism by the seaside, often on peninsulas reaching out into the Baltic. When I put the question, I was told that in these countries there was no feeling that the seaside was unsuitable for rheumatics and that "anyway our Baltic is more of a lake than a sea"!

Generally, in Europe I found a disposition in countries with a high proportion of coastal area to hold that "sea air" was good for the rheumatic patient; in countries with little coastal area, a disposition to recommend patients to get away from the sea; in countries favoured with extensive highlands, a tendency to attribute a good deal of importance to altitude as a favourable climatic factor. This suggested that a praiseworthy local patriotism had some influence in coming to opinions on this matter.

But on this question of climate there is no doubt that the incidence of rheumatic disease falls off definitely and sharply as one approaches the warmer climates. In Northern European spas one would always note patients exhibiting the stigmata of rheumatoid arthritis in varying degrees, but not nearly to the same extent in Southern Europe. (At Terme di Agnano, near Naples, the only case of rheumatoid arthritis I saw was in a German visitor.)

In the United States a centre for the treatment of rheumatic conditions has been established at Tucson in the desert climate of Arizona, for here indigenous rheumatism, though it occurs, is very rare. The results of sending sufferers from the Northern States to Arizona have not been so successful as had been hoped at first.

Very little positive scientific work on the influence upon rheumatic conditions of damp, of barometric pressure and of the nature of subsoil has been done abroad. Seegal (New York) has carefully recorded his patients' subjective response to changes in barometric pressure, with the result that there was no confirmation of the usual impression that the rheumatic patient can act as his own barometer.

From the evidence I would conclude that in the cool temperate countries—which are undoubtedly the chief areas, though not the only areas, marked by a great incidence of rheumatic disease—there is little definite importance to be attached to local climatic conditions. Certainly individual idiosyncrasies will allow some rheumatic patients to do better inland or in high country, and others by the seaside (the same principle seems to apply to asthma patients).

As to the value of rest in the major rheumatic diseases, I found general agreement as to its necessity, but in cases of ankylosing spondylitis there was a measure of disagreement on this point, which will be noted later. I was, however, impressed by Seegal's statement that merely to prescribe rest was insufficient, and that, if they were checked by careful and exact history-taking, the patients' ideas of the suitable length and nature of rest were often found inadequate. He holds that an exact prescription and description of rest is necessary when this is to be ordered.

Drug Treatments.—European and American treatment centres agree generally with British opinion that in the present faulty state of knowledge of the ætiological causes of rheumatic disease the use of drugs must be empirical and not specific.

Aspirin, or one other of the salicylate group, is the drug chiefly used in the treatment of rheumatism in all countries. Because of its antipyretic action in rheumatic fever, because of its analgesic property, because of its relative harmlessness and ready accessibility, it has won a place in the armoury of the attack on rheumatism that has scarcely been challenged. Throughout Europe and the United States I found aspirin being prescribed whether by the mouth, as in Great Britain, or mixed with bee venom and injected as " arthrorheumin " in the German clinics. Nowhere did I find any claim that it was curative or anything but analgesic, and in every country visited there was voiced the complaint, especially from those interested in arthritis, that their patients had been treated with salicylates for many months before seeking expert advice, and thus allowed to advance beyond the hope of adequate treatment and doomed to spend the rest of their lives crippled beyond the help of man. The view was expressed that, allowing full value to aspirin when rightly used, its employment to mask symptoms and to postpone adequate treatment until too late was a grave evil, against which

both medical practitioners and the lay public should be warned. Indeed, it was more than once suggested that a necessary task in planning a scheme of rheumatic treatment was to relegate aspirin to its proper place; not to regard it as a cure, but merely as a valuable adjuvant in relieving symptoms.

The use of gold in rheumatoid arthritis occupies a high place in the interest of those investigating drug therapy in rheumatism. Speaking broadly, its use is accepted in Europe, but viewed with scepticism in America. There is, however, a great divergence of views among those who advocate its use in Europe. Forestier in France, the pioneer in this method of treatment, has in his long experience worked out a dosage which is followed by the majority of those who use gold. In Scandinavia, France, and in Central Europe his technique is generally followed, and in Great Britain methods similar to his are usually accepted. Van Breemen and the *Forschungsinstitut für Rheumabekampfung* (Berlin) give minute doses, not usually exceeding 20 milligrammes, with a total course of only ½ gramme. Van Breemen spoke very strongly on this point, claiming that although gold was a valuable weapon in the treatment of arthritis, its use was being brought into disrepute by the ridiculously high dosage, with its attendant dangers, used by some.

At Professor Secher's clinic in Denmark (where the use of gold in treating tuberculosis was inaugurated, following Mollgaard's experiments) I found that he uses very heavy doses of gold in the treatment of that disease, giving as much as ½ gramme as an initial dose. But he told me that, such were the dangers of toxic manifestations of gold therapy in rheumatoid arthritis, he was tempted to abandon its use until he had elaborated a method of preventing such manifestations by the administration of very large doses of vitamins prior to giving gold injections. Vitamin C is chiefly used; vitamins A and B are also given; all in massive doses. Secher claimed thus to have obviated the dangers of gold toxicity. His conception of the nature of the toxic reactions following the use of gold is interesting; he believes them to be a manifestation of the disease process itself, and not of the toxicity of gold. He claims that Mollgaard did not get toxic reactions with "normal" doses of gold in healthy experimental animals, but did so in tuberculous animals, where the gold "liberated the toxins." In cases where the sedimentation rate is not elevated (*i.e.*, in osteo-arthritis) he claims that no toxic

manifestations occur after using gold; and that if toxic reactions do occur, and the original dosage is persisted in, the subsequent reactions will be smaller and will then cease, owing to the gold successfully combating the morbid condition. Secher is aware that his views are revolutionary and do not receive general support, and certainly they are not approved by other workers with whom I have discussed them.

In America the attitude of most of those interested in rheumatic diseases is characterised by a strong desire to "follow what is scientific and factual as opposed to what is empirical." This has led them to look askance at gold, on the mode of action of which there is no agreement. They point out that its use in chronic rheumatoid arthritis started from an analogy between that disease and chronic tuberculosis, an analogy which they cannot accept. They emphasise that its use is acknowledged to be accompanied by certain definite dangers.

American opinion is inclined to regard new-fashioned treatments which are based on theory rather than on scientific fact with an understandable cynicism. It is pointed out that they have seen so many such treatments have a short vogue and then pass into obscurity. Nevertheless, the continued use of gold in Europe and the many favourable reports published on its use are making their impression. Both at the Presbyterian Hospital (New York) and in the arthritis clinic of the Massachusetts General Hospital a serious attempt is now being made to investigate the value of gold in the treatment of rheumatoid arthritis.

There is in America little attention given to the use of sulphur in the treatment of rheumatism. American workers instanced it as an example of fads that had had their day and perished, pointing out that it was natural that those spas which had a proportion of sulphur in their mud or water emphasised this as a favourable point, but that they could give very little scientific proof of its value.

In Holland and in America an attempt has been made to assess the value of injections of salts of manganese in the treatment of forms of arthritis associated with psoriasis, but in both quarters the results had been disappointing.

A considerable number of workers have attempted to treat rheumatoid arthritis with prontosil, invariably with disappointing or equivocal results (though its value in gonorrhœal arthritis

is recognised, and is referred to later). Lately the newer form of that drug, M. and B. 693, is being tried out in certain cases of rheumatoid arthritis. It is too early yet to note results, but they will be awaited with interest.

ENDOCRINES.—Much interest is taken in several countries in the endocrine aspect of rheumatic diseases. In Holland both in Van Breemen's clinic (Amsterdam) and in Touw's clinic (Leyden) œstrogenic substances are being used in the treatment of certain forms of arthritis. At the Amsterdam clinic a careful "control" series was worked out by the use on the "control" subjects of inactive substances similarly administered, the physicians being unaware of whether they were giving the active or the inactive preparation. The results showed that 15 per cent. of the patients receiving the active preparation were improved, whilst none of those receiving the inactive substances showed any improvement at all. Rasmussen (Copenhagen), treating a series of cases with œstrogenous endocrine preparations, claimed to be getting good results. He is also attempting to stimulate ovarian function by diathermy. In Berlin also endocrines are used for the treatment of rheumatic diseases, as part of a many-sided plan of campaign rather than as a single measure. Œstrogenous compounds are given in small doses; at the same time other therapeutic measures are employed. It is not given in large doses as the main line of treatment.

It was at the Robert Brigham Hospital (Boston) that I found most enthusiasm for endocrine therapy of arthritis and other rheumatic conditions. Here Francis Hall has been interested for some time in arthritis occurring at the menopause and in castrates. He was so encouraged by his results in these types of patient that he went on to treat general patients suffering from rheumatoid arthritis, with many good results. He emphasises the necessity of large doses and uses 50,000 international units of progynon parenterally twice a week.

There seems no doubt that some patients are at least subjectively improved by the administration of œstrogens. But this by no means proves that the forms of rheumatism from which they suffer are due primarily to endocrine dysfunction. In diseases such as rheumatoid arthritis it is well known that all physiological functions are depressed, and the response to endocrine therapy in some patients may be merely due to the restitution of some function secondarily depressed by the morbid

condition. But, apart from true arthritis, there is no doubt that certain manifestations of the menopause, which by their nature may be termed rheumatic, are definitely improved by judicious endocrine therapy.

Foreign Protein.—The use of foreign proteins by injection is still advocated in many clinics for the treatment of arthritis; in this category comes the use of typhoid vaccine as a form of shock therapy.

Many types of foreign protein are used. Sterile milk is administered by Jarlov (Copenhagen), and he claims good results. Fehlow at the *Hubertus Krankenhaus* (Berlin) uses beef and pork blood. At the *Forschungsinstitut für Rheumabekampfung* yatren casein is extensively used in "all forms of rheumatism, including polyarthritis." They claim that when small doses of this are injected a local and general response is obtained and that the blood sedimentation rate and general condition of the patient respond well. Neuro-yatren, a mixture of non-specific staphylococcal vaccines with yatren, is also used there, and I found this preparation used likewise in Roumania, where they claimed favourable results, but do not regard the staphylococcal vaccines as in any way specific, but rather use them to produce a protein shock.

In America typhoid vaccines are used at many centres to produce protein shock in rheumatic diseases. They are so used at the Mayo Clinic. Crain of the Walter Reed Military Hospital (Washington) also told me he found them very useful. The drawback of typhoid vaccine has usually been that any improvement obtained has been only temporary, but modern physical and orthopædic measures may enable this improvement to be maintained.

I did not find that the use of bee venom had entirely died out. In Berlin they claim that it has a specific effect on the autonomic nervous system apart from the value of its histamine content. Similar views were held in Central Europe. But it is my opinion that bee venom therapy is one of the passing phases of rheumatic treatment.

Vaccines.—Vaccine therapy must claim considerable attention in any record of rheumatic treatments, for this therapeutic measure is claimed to have an ætiological basis.

Vaccine therapy is probably the most widely investigated and discussed form of treatment of rheumatic conditions (especi-

ally rheumatoid arthritis) in the world to-day. Some have rejected it after trial; others use it because they hope to see some of the wonderful results claimed by its sponsors; others are enthusiastic and regard it as truly scientific and based on a sound ætiological concept of the conditions. But in the minds of many other workers on rheumatic conditions, the prolonged use of vaccines is considered utterly unjustified and the concept to be based on erroneous and unscientific theories.

Vaccines used in the treatment of rheumatism are of different classes: they may be polyvalent; they may contain specific organisms only, or they may be autogenous. Here one is struck by the divergence of opinion among those who most vigorously uphold the use of this form of therapy, and the extent of this divergence is further emphasised when their ideas on ætiology are considered.

At Van Breemen's clinic (Amsterdam) more than 800 cases have been treated with stock vaccine over a period of many years. Plaat, who carried out the work, was very disappointed in his results. In Trencianske Teplice (Slovakia) Lenoch has used the same stock vaccine (an English preparation) and has been equally disappointed. Sideman (Chicago) used this vaccine on a large series and worked with controls. He had found an equal percentage of improvement in patients who had received vaccine and in the controls, and therefore could find no beneficial results from vaccine therapy beyond any psychological effect.

In regard to autogenous vaccines, more favourable results are reported. Jarlov (Copenhagen), who has done much work on this subject, claims good results from autogenous vaccines grown from dental infections in the patient, and his work has been favourably confirmed by other Scandinavian workers. In Sweden Sundelin reported that vaccines from intestinal streptococci had given ambiguous results.

I found the views of Reichert (Pistany) on vaccine therapy very interesting. He had made cultures from foci of infection and of intestinal streptococci, and had grown these cultures on ascites agar. With the vaccine prepared by boiling these cultures he had had some remarkably successful results; but these were in the minority of patients treated and, on the whole, he had been disappointed. He considered, however, that the explanation of why such good results could be obtained in some few

cases should be sought, and that therein lay the possibility of great benefit from vaccine therapy.

In the United States vaccines are very extensively used. In Johns Hopkins Hospital (Baltimore) the majority of patients attending the arthritis clinic receive hæmolytic streptococcal vaccines, and Wainwright is getting good results. At the Mayo Clinic vaccines prepared from non-hæmolytic streptococci from the upper respiratory tract by Rosenow are used to a considerable extent. Burbank (New York) has done much work on the bacteriology and serology of the rheumatic conditions, and uses vaccines as one of many methods of treating his patients. He reports much benefit derived from the correct use of this form of therapy.

The injections of dead organisms for the production of immunity to diseases they cause is a sound and proven procedure of preventive medicine. In rheumatoid arthritis we find that such injections of organisms are used by some workers as a curative procedure, although it is by no means generally accepted that these organisms are causative of the disease. There are many groups of workers using different organisms, each in the belief that the organism which he favours is responsible for the production ot rheumatoid arthritis.

To the unprejudiced observer, these facts make the acceptance of the soundness of this form of therapy difficult. Yet many who work with vaccines claim that their use is aimed at the desensitization of the patient to the toxins of that organism which produces his disease. Thus Rosenow claims that his vaccine contains antigen, but little or no toxin. At present it is very difficult to see one's way through the maze of vaccine therapy. In our present state of knowledge of the ætiology of rheumatism in general, and of rheumatoid arthritis in particular, the use of vaccines cannot be either endorsed or rejected. With a more exact knowledge of ætiology may come the definite establishment of this method of therapy.

Physical Treatments.—In Great Britain physical methods almost universally are considered to play an important part in the treatment of rheumatic conditions. In some centres for the treatment of these conditions, and particularly the spa establishments, physical methods are used predominantly and are considered the most effective for the treatment of almost all forms of rheumatism. There will be recorded observations on the use

in foreign countries of physical methods at (*a*) clinics not associated with spas, (*b*) spa centres.

One of the hopes entertained when this investigation was undertaken was that from the study of foreign methods of treatment there might be gathered data which would help to establish a standard form of physical therapy for the various rheumatic ailments. I found, however, that different foreign clinics disagreed with each other widely, and often emphatically, about the most suitable form of therapy for different conditions.

Taking lumbago as a stated condition, in Great Britain the infra-red rays are considered as probably the most valuable form of physical therapy. But in Amsterdam that condition is treated by ultra-violet rays; in Leyden by long-wave diathermy; in Denmark by cold wet packs at the *Bispebjerg* Clinic and by short-wave diathermy at the Finsen Institute. In all cases those ordering a particular treatment are confident that they are choosing the best method.

The therapeutic value of heat was almost universally acknowledged at all centres I visited, but the methods of applying it varied widely. Little emphasis, however, was placed on the value of physical therapy at the *Forschungsinstitut für Rheumabekampfung* (Berlin). Treatment of any form of rheumatism there is practically limited to various forms of injection therapy, and, beyond a little massage, almost no physical treatment is given.

Except at the spa establishments hydrology is very little used in Europe. At Amsterdam the hydrology room was deserted, as they had come to the conclusion that hydrological methods were not of sufficient value in treating rheumatism. In America, where I visited some lavishly equipped physiotherapy departments, I found that hydrology was considered to have its most valuable sphere in morbid conditions other than rheumatic.

To note now some observations on methods which seemed to me to be new. Rasmussen at the *Bispebjerg* Hospital (Copenhagen) said that he did not feel that heat alone was a sufficient stimulus of metabolism and circulation to warrant its extensive use as a physical agent; he had therefore developed a technique of cold wet packs which is now generally used in his department. Patients are first placed in a radiant heat bath for five minutes, and are then placed on a couch and wrapped in cold wet sheets; around these several dry blankets are rolled, and the patients

rest like this for an hour. The change from the radiant heat to the wet packs is momentarily unpleasant, but the patients soon become soothed, and a proper hyperæmia of skin and subcutaneous tissue is claimed to result. Professor Secher stated that he had himself undergone this treatment and had faith in it. At Skodsborg a modification of this method of therapy was used; hot wet packs took the place of the cold ones.

The Pittsburg (U.S.A.) School of Medicine, Department of Hygiene, has established a Research Fellowship in heat and fever therapy. Murry Ferderber, the Research Fellow, told me that he carried out animal experiments with various types of heat, and had found that moist heat increased the circulatory volume by 108 per cent. more than infra-red heat and by 62 per cent. more than the heat generated by short-wave diathermy. He had devised means of applying moist heat locally which are simple and safe. Although his work is by no means complete as yet, I think it is a valuable research into the physiology and therapeutic application of heat.

Fever therapy has been much discussed and developed during the last few years in the treatment of rheumatic conditions. One of its most useful applications has proved to be in the treatment of gonorrhœa and gonorrhœal arthritis. But just when its use and scope were being accurately worked out, the advent of prontosil and its derivatives in the sphere of chemotherapy gave promise of substituting methods as effective and much simpler than those of the difficult and complicated fever therapy. At the Mayo Clinic the demands on the fever therapy department have very considerably fallen off with the advent of prontosil. Nevertheless, those who worked with fever therapy have contributed a valuable advance to modern therapeutics, and there is little doubt that this form of treatment will still maintain a certain place. It is particularly in gonorrhœal rheumatism that fever therapy is most important, and I shall refer to it later in that regard.

Both Krusen at the Mayo Clinic and Ferderber at Pittsburg find a definite use for pyretotherapy in generalised arthritis, and Krusen holds that fever therapy in small repeated doses for the treatment of rheumatoid arthritis is easier to control, less unpleasant and more efficacious than injections of typhoid vaccine.

A recent form of physiotherapy is the application of deep heat by ultra-short-wave diathermy. On its introduction this

was hailed by some in Great Britain as a panacea, and I was interested to note how far it had established itself in foreign centres. It was generally considered useful and efficacious, but not as representing more than a slight advance over other forms of heat application. Ferderber of Pittsburg considered it inferior to moist heat in the production of increased blood flow. Many workers held that its greatest scope will be found outside the field of the rheumatic diseases and in the treatment of pyogenic infections.

In the use of X-rays as a therapeutic agent for arthritis considerable interest is being taken. In Copenhagen I attended a meeting of radiologists at which the topic for discussion was the treatment of rheumatism. The majority of these claimed that by the local and general use of X-rays the condition of rheumatoid arthritis could be rendered clinically inactive in 60 per cent. of cases. But their colleagues, not specialising in radiology, were not inclined to accept these results. At the Robert Brigham Hospital (Boston) Kuhns, however, regards local irradiation as valuable and successful in certain chronic and obstinate infective arthritides, which would not respond to other forms of therapy; and at the Finsen Institute much attention is being given to the application of X-rays to arthritis. This radiological treatment of rheumatic diseases appears to me symptomatic, and not based on an ætiological concept.

Occupational Therapy.—Occupational therapy in rheumatic disease attracts much attention abroad. In Great Britain until recently we have not been interested in this. In the Scandinavian treatment centres facilities for occupational therapy are always provided and are enthusiastically approved by the medical staffs. No great hospital in the United States is without its occupational therapists. At the Mayo Clinic particularly was I struck by the scope and value of this work. There, various types of apparatus are designed so that every joint can be brought into normal movement. Miss Pattee, the occupational therapist in charge, emphasises the fact that not only is active movement thus usefully obtained, but that occupation adds an interest to the lives of those patients whose physical disabilities might easily lead them into a life of miserable introspection.

Active and Forced Movements.—The value of stimulating movement (at the correct time) in rheumatic diseases is universally acknowledged, as the aim of all treatment is the restoration of

function. In Great Britain and in the United States—following our views on joint and muscle function—the use of forced movements is not considered beneficial except in a limited number of cases. But on the continent of Europe the use of power-operated machines of the Zander type to obtain forced movements is still common. One can see patients strapped into these machines and left with the power turned on. It seemed to me that either the range of movements obtained was within that of the affected joint, so that neither the machine nor the patient's muscles were subject to strain, or that, to avoid the inevitable pain and muscular resistance to the forced movements, the patients twisted themselves within their straps until the action of the machine was minimised.

Apart from such forced movements, the value of carefully graduated and supervised *active* movements is generally accepted in Europe and America. In Sweden at the *Nynas Kuranstalt* their value was strongly stressed and physical exercise every morning for all patients medically fit for it is compulsory.

In the American rheumatic hospitals the value of correct posture and postural exercises is emphasised, and patients are always instructed in these. The ideas originating from the Robert Brigham Hospital are being widely accepted. I do not, however, wish to give the impression that they insist on exercise as a continuous adjunct of treatment, but hold that it must come at the right time, be correlated with adequate rest, and not pursued beyond the limits of tolerance of the affected joints.

* * *

Observation of methods of treatment of ankylosing spondylitis showed certain points of disagreement. In England, France and the United States rest is usually described as the prime factor in the treatment of this condition. In Central Europe and in Germany movement is prescribed and persisted with. (I was not impressed with the results of such treatment.)

At the Robert Brigham Hospital (Boston) they follow a method of fitting plaster jackets, which limit abdominal and foster thoracic breathing. They seemed to be getting very good results.

Forestier in France is working on the treatment of ankylosing spondylitis by the injection of radon along the line of the vertebræ, and he claims that this renders the condition inactive. The

radon is injected subcutaneously with air along the affected areas in doses of 6,000 micromillicuries every other day until the patient has had between 60,000 and 120,000 micromillicuries. The patients who had had this treatment seemed to be enthusiastic about its effects. There is possibly some connection between this treatment and X-ray therapy of this condition which is being tried in England.

* * *

There have recently been two great advances in the treatment of gonorrhœal arthritis—first by fever therapy and then by chemotherapy with prontosil and its derivatives. Just at the stage when fever therapy had been explored and developed sufficiently to give satisfactory treatment for this condition, chemotherapy suddenly provided in prontosil a simpler and apparently equally efficacious method of treatment. It is possible now to review the situation in the light of recent developments.

In the United States, where fever therapy was elaborated, much work is now being done on the new chemotherapy, and it has been established that a minority of cases may be resistant to chemotherapy or to fever therapy. Both Dawson (New York) and Krusen (Mayo Clinic) found this. But a combination of chemotherapy and fever therapy seems usually to overcome even these resistant cases. Thus two rival forms of therapy seem to be able in alliance to overcome those forms of gonorrhœal arthritis which resist the powers of either singly.

III.—Methods of Treatment Abroad (Observations on Hospitals, Clinics and Spas)

To record now some observations on the various foreign spa centres visited.

Spa therapy in the treatment of rheumatic conditions denotes a great deal more than the physical use of certain muds and waters. It brings the advantages of dietetic and physical régimes, of change of climate and surroundings, and usually of mental relaxation. Thus spas have established for themselves in ancient and modern times a great reputation as healing centres for rheumatic patients, and have attracted a clientèle giving them unrivalled opportunities for the study of the ætiology, pathology and treatment of this group of diseases. Unfortunately not all the foreign spas make the best use of these opportunities.

One is forced to say that, with certain notable exceptions, the attitude of the foreign spa practitioner is that the mud or water of his particular spa, owing to minute differences in the sulphur, radium or other content, is superior to that of others, and alone provides a sovereign remedy for most of the ills to which the human body is heir; that the magic whereby such cures are effected is inherent in the spa water, independently of the ætiology or pathology of the condition; and that for the maintenance of health it is essential that at least three weeks of every year should be spent in "taking the cure" under the direction of the chosen practitioner.

So great is the faith professed in the efficacy of each particular spa water that at the majority of the spas I found facilities for administering it through every orifice of the human body. Thus it is given by intra-nasal atomisers for upper respiratory tract infection and sinusitis; by inhalation of vapour for bronchial conditions; by mouth for any hepatic or intestinal condition; by rectum for colonic irrigation; vaginally and urethrally where local conditions may seem to demand it; and, of course, the patient meanwhile takes immersion baths and drinks the waters.

Such claims probably have prompted certain American workers to deny categorically that spas have any important place in the treatment of rheumatism.

But there are spas in Europe where men of high calibre work, men who have not been bemused by the fact that they happen to work in localities where thermal mud and water abound, and who have approached rheumatic problems from a standpoint of scientific investigation. These are fully aware that spa water therapy is not the complete answer to the rheumatic problem. Such workers, taking true scientific advantage of the material at their disposal, can gather at their spa establishments most valuable knowledge.

The first spa visited was Varberg in Sweden. This is a seaside spa, open in the summer only. Here there is ample opportunity for physical therapy of standard types, but chief importance is attached to mud therapy. The method is to pack the patient with dark green sea mud, heated to 50° C. for twenty minutes. Afterwards the patient is immersed in sea water and the mud removed by washing him with bunches of freshly picked seaweed. In certain cases, instead of the mud, hot treacle is used for the pack.

The washing with seaweed is invariable. In some types of rheumatic disease hot mud packs are valuable. They provide moist heat, which stimulates the circulation, and the weight of the mud exerts a salutary effect on blood flow. Some also claim that if traces of radium or sulphur are present in the mud, these, too, are specifically beneficial. The use of fresh seaweed to remove the mud is probably founded on an idea of its iodine content having value.

The *Landesbad* centre at Aachen is sited around the thermal saline waters of that district. It is admirably equipped for physiotherapy and for hydrology with the local water, but owing to Slauck's theories of the ætiology of rheumatic diseases, what may be termed "spa treatments" takes a secondary place at this centre. They are used merely as a form of physiotherapy (probably their correct place). Slauck's theories of rheumatic ætiology (which have been noted in the chapter on ætiology) are not in any way influenced by the fact that he works at a spa. The *Landesbad* is a hospital for the treatment of rheumatic conditions among members of the National Socialist (Nazi) Party. It has about 400 beds, of which eighty are for women. Expenses are met by the Party. Those who cannot gain admission to the *Landesbad* stay at one of the numerous spa hotels in the city and are looked after by the local practitioners. They do not have the same opportunities for in-patient treatment or hospital and laboratory investigation. The chief interest of Aachen lies in Slauck's theories and the methods by which they are applied.

Aix-les-Bains is the foremost spa in France for the treatment of rheumatism. The State runs the spa establishment and receives the fees for treatment. The nature of the treatment to be received is prescribed by the member of the local *corps médical* whom the patient chooses and whom the patient pays independently of his treatment expenses. Private patients stay at hotels. The "cure" lasts from two to three weeks, and costs between 700 and 800 francs in the first-class baths, 400 to 500 francs in the second-class baths, and about 300 francs in the third-class. The nature of the treatment does not vary in these different classes, the difference being in the degree of luxury of the accommodation. Doctors' fees for private patients range from 400 to 2,000 francs, according to the means of the patient and the length of the treatment. A hospital, the Reine Hortense, is provided for the poor. This is an efficient, well-

staffed establishment. The maintenance fees in small wards are 32 francs a day, and in big wards 28 francs a day. In addition, patients pay about 2 francs per treatment received. The expenses of these poor patients are often paid by the various municipalities who send them for treatment.

The Aix spa treatments follow the various recognised forms of hydrotherapy, especially the well-known Aix douche. But hydrotherapy is not considered the complete answer to the rheumatic problem. As Jacques Forestier said to me: "We do not pretend to remove arthritis and ankylosis by hydrotherapy, but it is firmly established that the general condition and the resistance of the patient are improved thereby."

At Aix there is being undertaken an attempt to investigate the action of hydrotherapy by animal experimentation. At Forestier's suggestion, Professor Enselme of Lyons is working with guinea-pigs on their responses to treatment with Aix water and studying calcium and sulphur metabolism in bone and cartilage.

A recent instalment at Aix is a solarium designed solely for treatment with the sun's rays. It is controlled by Saidman and is of "windmill construction," the wings containing the cubicles, revolving to face the sun from dawn to evening. The different wave-lengths of the solar spectrum are applied therapeutically. It is an impressive structure, and likely to have distinct psychological effect on the patients treated. There is no doubt that the concentration of the sun's rays and the selection of such rays as the infra-red and ultra-violet can be of use in the treatment of certain rheumatic conditions; but apart from the psychological effect, I think that the comparatively cheaply and easily produced radiations from electrical lamps and some forms of gas heaters may be equal in efficacy.

Italian spas are regarded by the public more as centres where they can combine healing with pleasure—taking a holiday and "undergoing a cure" at the same time. There are many semi-quiescent volcanoes where the ground bubbles with a great variety of muds, hot waters, and gases. These are used with the usual techniques. The spas are State property, and facilities are offered for patients of modest means to "take the cure" reasonably. The treatment fees include the cost of the services of a physician. When I asked the physicians at Termi di Agnano about their conceptions of the ætiology and pathology of the

rheumatic conditions I was informed that they were chiefly interested in the correct application of their spa therapy and were not employed to spend their time in research. No hospital facilities are available, and this would naturally tend to make any serious research impossible.

Termi di Abano, however, is associated with the neighbouring University of Padua, and it was a pleasure to meet Professor Renosto, who worked at the University and the spa. He is an experienced pathologist, and has worked for a long time on the ætiological problems of rheumatism. The difficulties and negative results of such work had led him to devote himself to rheumatism from the standpoint of the clinician and therapist. He was therefore in attendance to prescribe treatment at the spa of Abano. It was my impression that the incidence of rheumatism, and especially of rheumatoid arthritis, is not so great in Italy as in the northern European countries. Perhaps this is the reason for the comparatively smaller degree of attention to research into its problems.

But on discussing this point with Dr. Paolo Ravenna, who worked with Professor Robecchi at Acqui, he told me that he felt that there was a considerable amount of both articular and non-articular rheumatism in Italy, but that the majority of medical men were not interested in it. At Acqui there is hospital accommodation for rich and poor, the latter being treated through their insurance companies. There is much more laboratory equipment here than at any other Italian spa, and a vast store of material not only in those patients seeking treatment at the spa itself, but also from the Casa Cottolengo in the neighbouring city of Turin, this being a large charity hospital for the poor suffering from chronic diseases. At Acqui they found themselves as uncertain of the true ætiology of rheumatoid arthritis as we do, but tended to regard it, not as a streptococcal infection, but as due to a virus. They also considered it as a separate entity from rheumatic fever. They regarded osteo-arthritis as a non-infective phenomenon, as the majority of workers in Great Britain do.

At Acqui they regarded spa treatment as dangerous in the acute phases of rheumatoid arthritis, but of great value in its quiescent stage and in osteo-arthritis. Of more specific treatments I found that they considered gold of great value, and that Ravenna and Rinaldi had been working on the use of sodium

glycerophosphate in rheumatoid arthritis. This is injected intravenously; it causes an almost immediate hunger, with subsequent increase in weight, and also gives the patient a pleasant euphoria. Ravenna, however, told me that he thought probably that the effects of this drug were more transient than those of gold.

In Roumania I met Professor Danielopolu, the foremost rheumatologist of that country. He works at the *Institut Cardio-Rheumatologique* at Eforia Tekirghiol on the Black Sea coast. He told me that the study of rheumatism has only recently been taken up in Roumania, and that the Institute is but three years old. It owes its situation to the abundance of radio-active mud and is conducted on the routine spa lines. Under Government control, the high fees of the rich contribute to balance the low fees of the poor.

Budapest is a spa enjoying certain special facilities. It is a University town with a flourishing School of Medicine; it is the capital city of the country, and it has a copious supply of mud and thermal water. The combination of these three circumstances is, I think, unique.

The various bath establishments in Budapest are owned by the municipality or by limited companies. The University and the medical profession help in staffing them. Hungary has been severely hit by recent economic conditions, and financial support is hard to obtain, but lately plans have been approved to establish a rheumatic research unit in one building. Such a unit, with branches in various hospitals, indeed already exists, having thirty beds under the direction of Professor de Pap for the study of rheumatism. Its effectiveness will increase considerably when all its work is concentrated under one roof.

The treatment at Budapest exploits fully the natural resources of the spa, but by no means is this regarded as the alpha and omega of rheumatic treatment. Every suggested form of therapy is carefully examined and used if it proves valuable. Research is actively encouraged, and as high a scientific standard is maintained as is possible.

The commonest way of meeting expenses of the cure at Budapest is to pay a lump sum for the "all-in cure." Prices vary from £15 to £30 for three weeks' accommodation, medical attention, and treatment. There is one criticism which cannot be avoided—viz., that there is nothing to prevent patients ordering their own treatment without medical advice. The medical

profession are naturally opposed to this system, and if the patient is allowed to order vigorous thermal treatment for himself without medical advice, it is not surprising that undesirable results sometimes occur.

The spa at Pistany in Slovakia offered an interesting comparison. At Pistany the whole of the spa establishment, including the hospital buildings and the hotels, was at the date of my visit (it may be different now) owned by the Winter family. At first it seemed anomalous that a medical institution should be owned and directed by laymen, but clearly there was admirable control of the facilities for treatment. It was the aim of the Winter family to provide accommodation and effective treatment for all pockets, and in this they succeeded. In contrast to Budapest, the spa owners will allow no one to take any form of treatment except under medical advice; all doctors practising in Pistany are allowed to order treatment. The hotels vary from the *de luxe* type to very comfortable and moderate establishments for the poorer patients. In addition, there is a 600-bed hospital for the treatment of insured patients suffering from rheumatism. Thus all classes are well provided for.

Perhaps the situation with regard to the medical fraternity is not quite so satisfactory. A number of sincere, intelligent, and scientifically honest physicians practise in Pistany, and with them I had many interesting discussions on rheumatic diseases. But there are also some physicians who maintain nursing homes of their own and conduct them somewhat in a commercial spirit. Their interests do not seem to go much beyond exploiting the facilities of the spa.

In the Pro Patria Hospital, where the insured patients were treated, Kollar is the physician in charge. He is a whole-time worker, paid by the spa owners, who provide him with every facility for therapeutic research. Careful examination and full investigation of every patient is made. The average permitted stay of three weeks is, however, regarded by the medical staff as being far too short. It hampers the adoption of effective therapeutic measures for severe chronic cases.

Two points impressed me on my visit to Pistany: firstly, that enlightened private ownership of such an establishment can prove benevolent and helpful to medicine and science; secondly, that the co-operation of insurance societies can be obtained and maintained on a mutually satisfactory basis. It is to be hoped

that this valuable institution has not been prejudicially affected by recent political changes.

The neighbouring spa of *Trencianske Teplice* (the hot springs of Trenc) does not aim to attract foreign support, nor does it offer, as does Pistany, a variety of holiday attractions. Private patients stay at hotels which are not financially connected with the baths establishment. This is municipally owned. There are several sanatoria owned by the Public Utility Corporations, such as the State railways. One-class accommodation and treatment are provided for employees requiring it. The system of treatment centres round mud and hydrology, and needs no special description. Franz Lenoch, the physician in charge of the establishment, is a man of scientific mind, and is highly regarded by the profession in his country. He investigates the efficacy of all forms of treatment. He told me he had been disappointed in vaccines, but encouraged by gold.

Trencianske Teplice, relying solely on its own nationals as patients, was enjoying a busy season in spite of the international situation. It is held in high regard by the medical profession of the country.

* * *

To note now the work at foreign treatment centres not associated with spas, but with general hospitals or with sanatoria, or carrying on as clinics devoted solely to the treatment of rheumatism.

The *Instituut voor Physische Therapie* (Amsterdam) is an out-patient clinic for the treatment of patients suffering from rheumatic diseases. Its income is inadequate, and it is housed in an unsuitable converted building, but its staff is notably strong. The director is Van Breemen, whose enthusiasm and self-sacrifice in the cause of combating the rheumatic scourge are known throughout the world. He has an enthusiastic group of whole-time workers and outside consultants to assist him. The equipment is good for physical therapy and for investigation. But the workers all agree that they are hampered by the lack of in-patient facilities for investigation and treatment, and regret that the health authorities do not co-operate in providing such facilities.

Two types of patients pass through the Institute—insured patients referred by the insurance companies, who pay for their

treatment at an inclusive rate (about 5,000 of these are treated annually), and private patients referred by general practitioners for consultation and treatment if necessary. It is pointed out that these patients are often referred at a far later stage than they should be. About 200 private patients are seen annually. The uninsured poor are not treated here. Although described as an Institute for Physical Therapy, treatment is by no means limited to physiotherapy; all suggested forms of treatment are investigated and carried out if deemed advisable. Physiotherapy, however, plays a large part. Research facilities are limited by inadequate accommodation and by the absence of in-patients, but, nevertheless, much valuable work in the investigation of therapeutic measures is being done. A careful survey of housing and other home conditions as promotive factors in the rheumatic diseases has also been carried out. The Institute has the advantage of being the headquarters of the *Ligue Internationale contre Rhumatisme*.

The *Forschungsinstitut für Rheumabekampfung* (Berlin) is a somewhat similar establishment. As its name implies, it is a centre for investigation into the treatment of rheumatism. (Again it is inadequately housed in a converted building.) Its staff, led by Professor Julius Rother, work on the treatment of rheumatic diseases more by chemical and endocrine than by physical treatments. Ætiological research is not carried out. The Institute treats the insured poor and patients referred to them by the Party Arbeitsfront, which has a central medical bureau for all workers needing medical aid.

The Scandinavian countries are well known for their provision of sanatoria for the investigation and treatment of rheumatic diseases. The first of these I visited was the *Skaelskør Gichtsanatarium* on the island of Seeland in Denmark. (*Gicht* [gout] is synonymous with rheumatism in Scandinavia.) This sanatorium was built in 1934 by the insurance companies. It accommodates 128 patients, who come from all over Denmark; there is always a waiting list. The equipment and general arrangements were impressive. There are physiotherapy departments adjoining the wards on all floors; complete laboratories; a very pleasant sun roof and an adequate department of occupational therapy. Its situation, near an inlet of the sea, seemed to me bleak and windy, and also it appeared to be understaffed. The medical staff is led by Nyfeldt, who carries on researches on

the relation of focal infections in arthritis and on the artificial production of arthritis in rabbits by bacterial inoculation.

Patients sent by the insurance companies stay for three months on an average. The value set on its system of treatment may be assessed by the fact that there is always a waiting list of patients. Treatment follows the usual lines prevalent in European establishments not in the spa class, being a combination of drug and hormone therapy and physiotherapy. The range of drug therapy is comprehensive; I saw patients, for instance, who had had gold, then arsenic, then prontosil, then campolon.

The *Nynas Kuranstalt* (Nynashamn, Sweden) is a modern 250-bed sanatorium for the treatment of chronic diseases; almost all the patients are rheumatic. It is owned by the State Insurance and Pensions Board. The main hospital block faces south-west, towards the sea, and contains the wards, treatment rooms, occupational therapy rooms and recreation rooms. I was much impressed by the thoroughness of the records, which included a footprint of each patient. Moreover, the "follow-up" system is admirable, the patients returning at regular intervals for re-examination and further treatment if necessary. The medical staff is headed by Dr. Sundelin, a keen and painstaking worker. His knowledge of rheumatic problems was obviously thorough, and he was familiar with all forms of physical and chemical therapy. He told me that, as this was a centre for the rehabilitation of chronic invalids, he had the responsibility of deciding when his patients could resume their occupations. In coming to decisions on this point he had been helped by instituting a system of intelligence tests which often showed interesting indications in regard to those patients who did not seem to be responding to therapy. This struck me as an interesting point. Many clinicians in this country agree that cases of rheumatism do best when those who are treating have the keen co-operation of those who are being treated. In certain cases where the patients adopt too passive an attitude, treatment is apt to be less effective. Sundelin found that such a type was liable to show an intelligence quotient below the normal. The large gymnasium is a feature of the Nynas Kuranstalt. There, when permitted by the medical staff, the patients carry out gymnastic exercises with a typically Swedish enthusiasm.

The *Hubertus Krankenhaus*, with thirty beds, is Berlin's centre for the in-patient treatment of rheumatic diseases. It is

under the direction of Dr. Fehlow. As it is conducted in association with the *Forschungsinstitut*, physiotherapy is very little used. Dr. Fehlow's conception of the rheumatic diseases is that they are the result of many causative factors, such as focal infection and endocrine and metabolic disturbances; and the patients receive treatment based on these lines. It is the view of the workers at this centre that the condition must be treated fundamentally and ætiologically, and not merely symptomatically. This, of course, is entirely in accordance with British ideas, but, as such difficulty is found in building up a conclusive ætiological concept of the rheumatic diseases, treatment, according to the British point of view, must be largely symptomatic until causative factors are clearly decided. The director is keen, enthusiastic and extremely hard-working, but I was not always able to follow his facile explanations of the ætiology of the cases he was treating.

The Robert Brigham Hospital (Boston, U.S.A.) has 150 beds for the treatment of chronic, but not incurable, diseases; the majority of the patients suffer from rheumatoid arthritis.

It was founded by a charitable bequest, and the fees paid by patients are kept as low as possible; patients from the immediate vicinity may be treated free. The equipment is very fine, and everything is provided that might possibly prove beneficial to the patient. The staff consists of orthopædic surgeons and physicians, and it was of value to note the close co-operation in treatment between these two groups. I was particularly impressed with the spirit of optimism that pervades the hospital; the psychological value of such a spirit in the treatment of rheumatism is amply proven.

It is to the group led by Osgood and Swaim at this hospital that we owe much of our knowledge of the valuable help that can be obtained from orthopædic measures in rheumatic diseases, especially rheumatoid arthritis. The cardinal points in treatment there are that rest is an essential form of therapy for rheumatoid arthritis; that correct posture is essential for the restoration of normal joint metabolism and function; and that rest and correct posture can be very largely achieved by their technique of plaster-of-Paris splints and casts. Of the value of this scheme of therapy there can be no doubt. Rest is being considered more and more important in treatment, and the value of splintage has been established throughout the world.

Much valuable work also is being done in surgical intervention for the repair of deformity. But it is fully understood that the mere straightening of deformed joints does not necessarily lead to restitution of function if other factors are not considered. Such is the success of the methods employed at this centre that figures show that 85 per cent. of patients treated are able to earn their living after discharge.

The "follow-up" of former in-patients is carried out with admirable care. As far as the wishes of the attending staff go, no patient, once admitted, is allowed ever to feel that the hospital has washed its hands of him. Patients are encouraged to return for periodical "check ups," and are taught to regard the hospital as a centre for advice on medical and general problems arising from the fact that they are suffering from articular rheumatism. Very much can be learned of the care of the arthritic from a visit to the Robert Brigham Hospital.

General hospitals in foreign centres vary greatly in their attitude towards rheumatic patients. Many have no special departments to care for them and the patients are treated by the general physicians. In other hospitals they are cared for in the departments of physical medicine, and these departments commonly develop into rheumatism clinics, although not specifically so termed. It is not necessarily to the disadvantage of the patient that a hospital has no special department for dealing with rheumatic complaints. In several hospitals which I visited the general physicians had a particular interest in rheumatic problems, and devoted many of their beds to rheumatic sufferers. But it is also true that in some general hospitals the sufferer from rheumatism can evoke no especial interest, and is passed from one department to another until he loses the hope of relief.

The *Bispebjerg* Hospital (Copenhagen) is an impressive establishment built on the pavilion plan, with beautiful lawns and gardens between the numerous single-storey ward blocks. On my expressing admiration of this to Professor Secher, he assured me that it might be beautiful, but it was certainly inconvenient and uneconomic, as imposing many miles of unnecessary walking on the medical and nursing staffs. Here the sufferer from rheumatism is cared for in the general wards by Professor Secher (who is greatly interested in such diseases and is a protagonist of gold therapy) and by Rassmussen in the department of

physical medicine. No rheumatic sufferer could complain of lack of interest in his care at the Bispebjerg Hospital.

The *Almindelig* Hospital (Copenhagen) corresponds closely to our rate-supported hospitals. It is fortunate for the rheumatic patients that Dr. Ejnar Jarlov is particularly interested in their cases. Treatment here follows the lines usual in Great Britain.

In New York the modern hospitals are vast institutions built on the "skyscraper plan." This assists centralisation, and the ample provision of high-speed elevators reduces to a minimum the time spent on travelling from one section to another. The modernity and the lavishness of their equipment are remarkable. In spite of economic depressions, far more money is made available in America for medical equipment and research than is the case in Europe.

At the Presbyterian Hospital, the "Medical Centre" (New York), there is an arthritic department under the directorship of Dawson and Boots. These are general physicians with a particular interest in arthritis, especially in its ætiological problems. They are inclined to deplore the multiplicity of new treatments for the rheumatic diseases, which they point out—under present conditions of deficient knowledge of rheumatic ætiology—are not founded on scientific concepts of the causes of the disease. They are convinced that the majority of such treatments are valueless and can only have an ephemeral vogue. Their scepticism about theoretical concepts of disease and insistence on scientific fact was refreshing after some of the glib but unconvincing theorising met with in some other quarters.

The methods employed at this centre, both in the ward and in the out-patient clinic, are "to study the natural history of the disease until we can get some facts on which we can work." The directors consider that rest, adequate diet and general management will do as much for arthritis as any specific therapy. This clinic is essentially "arthritic," and as such does not have referred to it cases of non-articular rheumatism. It was here that were expressed most strongly the doubts entertained by some Americans about the existence of fibrositis. But in the "arthritis clinics" the physician in charge, usually working on a full-time basis, sees only cases which have been previously "picked and sorted"; therefore, he does not have referred to him the cases of non-articular rheumatism with which we are so familiar, as these are not cases of arthritis. Personally I

feel that as much fibrositis occurs in the United States as in England.

On Welfare Island (New York) a large hospital has just been built for the care of chronic invalids. This is partly staffed from the Presbyterian Hospital, and under Dr. Seegal there is an enthusiastic group of workers engaged in research work on the chronic diseases. A considerable number of arthritic patients are observed here for periods extending even up to three years (contrast this with some hospitals in Europe where a patient is fortunate if he gets more than three weeks' hospitalisation). As at the Presbyterian Hospital, the objective of the work in rheumatism is "to study the natural history of the disease," and this study is intensive. Not only is the laboratory investigation very thorough, but much psychological research is being carried out.

The New York Hospital has recently been rebuilt, a lofty white building by the riverside. One of the leading physicians, Cecil, is greatly interested in the rheumatic diseases, and much research work on their ætiology has been done. Associated with him in the arthritic clinic is Angevine, who works both on the clinical and pathological aspects of the rheumatic diseases. I noted a willingness to investigate the claims of drug and other methods of therapy of the rheumatic conditions. Much valuable work on infective theories of causation of rheumatism is being done here.

At the Massachusetts General Hospital (Boston), which is staffed by the teaching staff of Harvard University Medical School, there is a group working under Dr. Walter Bauer, endowed for research into chronic rheumatic problems. The work being done here is remarkable. Ætiological problems are kept in the forefront, and the disease is studied from every possible angle. There is a State scheme in the Commonwealth of Massachusetts to provide for the treatment of arthritic patients. This supports twenty beds, and patients may stay for periods up to six months. Work goes on simultaneously on the ætiology, cytology, pathology and chemistry of the rheumatic diseases. This "arthritic clinic" admits only patients who have been through the wards, for it is thought that a complete knowledge of the patient can only be obtained in this way. Treatment follows general methods, with special attention to posture and postural exercises.

At the Johns Hopkins Hospital (Baltimore), relying on the

fact that work in New York had shown that the serum of a majority of the patients suffering from rheumatoid arthritis would agglutinate hæmolytic streptococci, treatment of this condition is carried out almost entirely by means of injections of streptococcal vaccines.

At the Abington Memorial Hospital (Philadelphia) Pemberton carries on work which has won for him a world-wide reputation. He takes an extraordinary degree of care over every detail in the investigation and treatment of his patients. His treatment is directed towards the thorough eradication of " septic foci " and the maintenance of healthy function of all the body, especially the large intestine. Research work on the biochemistry of the plasma proteins is being carried out. Pemberton's enthusiastic devotion and attention to the minutiæ of his patients' troubles earn him their respect and confidence.

The Mayo Clinic presents a picture different from that of the hospitals already described. It is essentially a consultative centre, where specialist advice on diagnosis and treatment can be obtained. It is not, as most hospitals are, situated in a district where it can serve its patients by continued attention. The majority of patients arrive from other districts, receive advice and depart. There are admirable hospital facilities in connection with the clinic, but most patients are not prepared to avail themselves of these, except, perhaps, for a few days during which certain essential investigations can be carried out. The numbers passing through the clinic are truly prodigious, and a wealth of material is at hand for research purposes. The arthritis section at the Mayo Clinic, which is directed by Hench and Slocumb, is therefore faced with somewhat different problems from those met by other American workers. Their patients usually do not expect to be admitted to hospital for a course of treatment, but come for diagnosis and advice just as they might in England consult a specialist who would advise their family doctor. But among the very great numbers of patients who pass through the clinic there are some willing to undergo hospitalisation, and the beds controlled by the section are always full of patients presenting interesting problems of diagnosis and treatment. Thus much can be learnt at the Mayo Clinic of great value in the therapeutic sphere. There is also available a great volume of results of scientific research on ætiology. (The section on ætiology shows how wide their researches have been in that direction.)

Treatment prescribed at the Mayo Clinic is based on broad lines. The general resistance of the patient is built up by high caloric, high vitamin diets; septic foci are removed; physiotherapy and non-traumatising exercises are used for affected joints, and vaccines are considerably employed to desensitise the patients to the toxins of harmful organisms. But it is in advice on after-care and on home methods of treating rheumatic diseases that the arthritis department of the Mayo Clinic is particularly noteworthy.

A careful and exact "home-therapy" scheme has been elaborated at the Mayo Clinic. A large proportion of patients are Mid-West farmers, who have access only to small towns where opportunities for physiotherapy and other treatments may be unobtainable. The Mayo Arthritis Clinic, therefore, assisted by the physical medicine department, has developed a system whereby the patient is educated in the causes and care of his own disease. He starts his visit to the clinic by attending a course of three lectures given by the medical staff, and illustrated by films, on the causes and cure of rheumatism. This is sufficiently elementary and dogmatic to appeal to the lay mind (and not of negligible value to the medical practitioner; I derived no small benefit from attending the course). The patient is carefully instructed in such matters as diet, rest, clothing and exercise in so far as they affect rheumatic diseases. Furthermore, with the co-operation of the department of physical medicine, a system of simple but effective home physiotherapy methods has been evolved. Those whose homes are without electricity are shown how heat therapy can be carried out by means of "bakers" using solidified petrol. Simple radiant heat lamps and baths for home use are described in detail, and uncomplicated but yet effective means of carrying out physical treatments, where expert care is not available, have been admirably designed.

The department of occupational therapy plays a valuable part in this system of home treatment and after-care; patients are instructed as to what work about the home or farm will benefit their particular case and what will be harmful. Thus the patient who returns home from the arthritis department of the Mayo Clinic, and who may not be within easy reach of expert advice and treatment, has been well educated in his own care. The trouble taken in planning this scheme is rewarded by the interest and gratitude of the patients.

Admirable is the degree of care of out-patients of the American Rheumatism Clinics. This is provided by the devoted work of social service workers, usually women University graduates. The home conditions, the means of livelihood, the diet and the habits of out-patients are investigated. The workers are well trained and, with a knowledge of economics, dietetics and hygiene, are able to report and advise expertly. Naturally, in its operation such a system meets with a certain amount of criticism as being unduly "interfering." But this criticism is rarely met with and never justified. The social workers have no aim but the benefit of the patient. Through this social service patients who have neglected their treatments can be traced and charitable funds justly distributed. Above all, the clinics can keep in touch with their patients. This, in the treatment of rheumatic diseases, is of prime importance; the co-operation between physician and patient should be thorough and long-continued. The Americans can give us valuable guidance in after-care and supervision of the patient who has sought expert advice.

Bringing now to a conclusion this survey of systems of treatment abroad, and before entering upon a discussion of what lessons may be learned from them, I may note an interesting American system for treatment of traumatic rheumatic manifestations of an occupational origin. In doing so, I wish to emphasise that I record the facts from the point of view solely of a medical observer, without any suggestion of criticism of British industrial social welfare arrangements, which, in my opinion, are as good as any in the world.

I was fortunate to have an introduction to Dr. William O'Neill Sherman, Surgeon-in-Chief of the medical services of the vast United States Steel Corporation at Pittsburg. He practises now largely as an operating surgeon, but is also concerned with traumatic rheumatic manifestations occurring among the employees of that Corporation. These aches and pains following trauma are of common experience in heavy industry, and can prove very expensive to health insurance schemes. Usually heavy industry in the United States pays an amount annually equivalent to 8 per cent. of its wages bill in sickness compensation. The United States Steel Corporation has reduced the rate to 3 per cent. This has been achieved, in Sherman's opinion, by the employers taking over all medical care. Patients

injured at their work are treated in the firm's own hospitals and wards. The patient is not made to feel that, as he is injured, the employer wishes to be rid of him. He is given to understand that his job awaits him as soon as he has been restored to health. This psychological approach to the patient, Sherman stated, has proved most successful, and the majority of sufferers return to full work even after long periods of incapacity.

Certainly an industry which, on account of its conditions of working, is liable to an increased incidence among its employees of rheumatic (or any other) disease follows the lines of both wisdom and justice in seeking to organise preventive measures (in so far as they are possible) and the promptest and best curative measures. I think this is widely recognised in many industries in Great Britain, and voluntary good-will in this field is reinforced by measures of social legislation. But control by the employing firm of medical treatment of its employees may have objections, not so much on medical as on other grounds. It seems to me that the system developing in our mining industry, whereby the employers and the workers co-operate in this matter, and control is largely in the hands of the workers, is better. But that is perhaps outside the province of a medical observer. One clear conclusion can be drawn from the Pittsburg experience—the great economic benefit of organising prompt and efficacious treatment of morbid conditions arising in industrial occupations.

The next section will endeavour to summarise the practical suggestions to British Treatment Centres which may be gathered from the observations noted. Obviously those suggestions may be influenced in some degree by my personal opinion, and others may attach more importance to a different set of facts (or theories). What I have tried to do is to record fairly all that came to my notice, aware that all may not make from them the same deductions.

IV.—Recommendations for British Treatment Centres

Before setting out on this investigation of foreign Treatment Centres and their methods I had entertained the hope that it would be possible to attempt some check, however tentative and imperfect in form, of results achieved by different centres. The great advantage is obvious if one could report that in such-and-

such a centre certain methods are given a paramount place, in another centre other methods, and that reliable statistics of results suggested that the methods of one centre were apparently more successful. Unfortunately, I found that there was no prospect of coming to any conclusions on that point which would have the slightest scientific value.

The root of the difficulty is the lack of precise knowledge of the ætiology of the rheumatic diseases. Lacking that precise knowledge, various workers pin their faith to various methods, and are apt to claim as a result of their own methods a standard percentage of improvement or of cure, usually from 60 to 70 per cent. The claim has usually this much basis of correctness: that there will be always a great number of cases which will show good results from rest, from general régime, from the confidence which can be inspired by the practitioner; and these results are quite irrespective of particular methods of medication, inoculation, etc. Indeed, in America I encountered more than once the somewhat cynical comment on recorded results of any method: "Oh, the usual 70 per cent. of improvement."

Further, there is the bewildering confusion in the classification and nomenclature of the rheumatic diseases. What is diagnosed at one centre as a certain condition may be diagnosed quite differently at another centre. Finally, there is rarely attempted anything like complete records of case histories (I except from this some centres which are giving close attention to what they term "the natural history of the disease"). Thus there can be no attempt at a comparative check of results attained by varying systems of treatment.

The lesson is that, in a national plan of treatment in our country, the importance of full and clear records should be kept in mind, and these records should be based on an agreed classification and nomenclature. Some are inclined to regard this as "mere paper work" and a waste of time. But it is essential for any attempt at standardising treatment to have definite knowledge of the results of various methods.

In securing that definite knowledge, any system of records is liable to be affected in some degree by that "confidence in the practitioner" mentioned. It is a commonplace that a medical attendant who has supreme confidence in his own methods, and can inspire patients with that confidence, will obtain successful results, which another might not get from the same methods.

This, the psychological factor, plays a most important part in the treatment of diseases the actual causation of which is still obscure. (It does not apply, of course, to any extent in the treatment of those diseases of which the causation, whether bacteriological or biochemical, has been positively ascertained, and the treatment of which is a matter of skilful and careful routine.) It is specifically important in the rheumatic disease. The rheumatic patient, with a chronic and often crippling disease which gives him great opportunities for introspection and self-pity, if he is treated by a physician who inadvertently betrays his belief that nothing much can be done, reflects that attitude. But if the physician is obviously keenly interested and full of confidence, the patient almost invariably responds. It is for this reason that physicians using very different methods can achieve success, even practitioners considered by the majority of the profession to use unscientific and unorthodox methods, but who yet can win the trust of their patients. Sideman of Chicago impressed me with the statement that he had carefully assessed the influence of his own moods on his arthritic patients, and found how easily either his own discouragement or hopefulness could be reflected in them; and Burbank of New York told me that he sought primarily for subjective and not objective improvement in those he treated.

The most careful system of records could not wholly eliminate from its results this psychological factor, though it would do so to a large extent, as, presumably, a method of treatment would not be accepted as "standard" unless it proved successful in the hands not merely of an individual or of a small group of workers, but in general use.

Nothing in the above paragraphs should be interpreted as implying any derogation of the confident practitioner who can heal by measures which are not generally successful. We are discussing methods applicable on a national scale; and that means methods which can be learned and efficaciously applied by every skilful doctor.

Education in Self-Help.—In planning treatment on a national scale in Great Britain—defining that as to make available for all sufferers the most effective means of relief, and to all threatened sufferers the most effective means of prevention—the most useful guidance appears to me that gathered from American observations.

Education in self-help is the leading feature in the best efforts there to combat the ravages of rheumatic disease. That is no novelty in medical practice; the great physicians of all times have accepted as their guiding principle that in dealing with disease afflictions generally the most efficacious course is to rally to their aid a determination on the part of the patient to get well, and to enlist this determination in assisting the healing forces of Nature. Drugs and other adjuvants have their highly important place, but are often secondary to promoting the will to recover. In the rheumatic diseases, especially in their early stages, this is always true; and even in the later stages it is usually most helpful, though the cruelty must be avoided of attempting to insist in hopeless cases on efforts of self-help which are probably useless and certainly painful.

The rheumatic diseases, however, present particular problems in this regard, for there are, among the great mass of sufferers, two sections, both fairly large in numbers, who have to be given special measures of attention, guided by opposite considerations. There is the section suffering—or imagining they are suffering—from aches and pains which they think justify a restful and, on the whole, not unpleasant term of treatment; there is the section which is disinclined to take the warnings which skilful diagnosis would detect as clear indications of the onset of dangerous rheumatic disease. It is, therefore, of prime importance that education in self-help should be under sound direction. "Sound direction" would be the key to successful results. Such direction would keep its advice strictly to simple, well-proved matters; would discard all empirical experiments, and avoid reference to methods which had any element of danger to the patient. The purpose would not be to encourage self-drugging or self-experimentation (*e.g.*, with radiation treatments, some of which are dangerous and some useless), but to instruct the sufferer how he or she can co-operate in a carefully explained plan of remedy.

The methods adopted at the Mayo Clinic arthritis department (noted in Section III.) seem to me a good model to follow in the treatment of rheumatic disease in Great Britain. Some modification of those methods to meet differing national conditions of living would be necessary, but I believe that the general idea is sound, and that a British scheme of treatment could usefully seek to develop "home therapy," based in the

first instance on sound advice and subsequently safeguarded by periodic supervision of the patients. Many of the rheumatic treatments are expensive in time and in money. If the number of treatments at clinics can be largely reduced by the substitution for some of them of such "follow-up" methods as can be followed in the home, the economy would be great. But there must be the effective safeguards that such home measures are in the first place soundly advised, and in the second place kept subject to skilled supervision at proper intervals.

The organisation of such a system would be a task the difficulties of which would be justified by the results. Its basis would be the preparation of good educational material—in films, in lectures, in leaflets. Its executive working staff would be district Treatment Centres, adequately staffed for diagnosis, for methods of treatment, for education in home therapy, and for the necessary degree of supervision of patients in their homes and their places of employment. A great part of this supervision could be entrusted to social service workers with the necessary degree of knowledge.

The great desideratum in dealing with the rheumatic sufferer—or the individual who is diagnosed as predisposed to rheumatism—is that he or she should be able to continue in normal occupation and recreation; should be spared, to the degree possible, visits to clinics; but at the same time should be safeguarded against drifting into serious disability, either from the lack of remedial measures or from following wrong methods. "Home therapy," under careful supervision, would help greatly to attain that desideratum.

Climatic Conditions.—Whilst it is generally accepted that the subtropical and tropical climates have a very small indigenous incidence of rheumatic disease, this may be due partly to other living conditions than those of sun temperature—*e.g.*, to diet and clothing habits; possibly, also, to the rarity of rheumatic infective agencies in those regions. Rheumatic disease thus may be in its incidence largely a "disease of civilisation," promoted by the living conditions of great aggregations of population. As noted, an American experiment of removing rheumatic sufferers to a hot, dry climate, contrary to expectation, has given no definitely encouraging results.

From the evidence collected I should conclude:

(*a*) That there is no necessity to attach great importance to

the locality of a rheumatism treatment centre, whether it is by the seaside or in an inland, hilly district.

(*b*) That whilst an individual patient will often, as in many other morbid conditions, benefit by a change from one climate to another, this does not warrant a general rule seeking to banish sufferers from any particular localities. For the great majority, the prospects of relief or cure are equal wherever they live, provided that they follow as sound a hygienic system as possible in regard to clothing, shelter, etc.

Rheumatism Treatment Centres should, as part of their system, give simple and practical advice to patients as to how they can take safeguards against the climatic conditions of their locality. This advice could be based on a set of general principles with modifications for particular localities.

Occupational Conditions.—Obviously some occupations are specially promotive of many of the forms of rheumatic disease. Such occupations are those which:

(*a*) Diminish the amount of sunshine and fresh air.

(*b*) Impose constant repetitive movements bringing into play only a small section of the muscular system.

(*c*) Impose cramped positions at work.

(*d*) Subject workers to quick alternations of heat and cold, or to constant wet conditions.

(*e*) Subject workers to frequent minor bruising and tearing injuries.

A detailed investigation should be set afoot into the conditions of industrial occupations which are especially promotive of rheumatic disease, with a view to drawing up a plan of practical advice for each industry concerned as to how such promotive conditions can be best avoided or mitigated, or their consequences relieved by remedial measures.

Rheumatism Treatment Centres should, as part of their system, note occupational factors appearing to affect their patients. Such notes should be communicated to those in charge of the investigation suggested above. Rheumatism Treatment Centres should give advice to their patients, where occupational factors are concerned, as to simple measures of precaution (such as physical exercises) which could be remedial.

Knowledge of the principles of "occupational therapy" should be gained by practitioners treating rheumatic patients.

PHYSICAL TREATMENTS.—There was observed in foreign centres practically general agreement as to the value of heat, massage, and radiation for the rheumatic sufferer, with some differences of opinion as to methods and degree of application. The evidence collected suggests, in regard to heat, that there is no reason to believe that the more elaborate and fanciful methods, calling for some special apparatus or some particular medicated mud, are more effective than simpler means, except to the degree of psychological effect secured. On this point of the application of local heat it is my view that under a system of education in self-help, under skilled supervision referred to previously, it may be possible to make greater use of home application of heat. It is, of course, by no means uncommon in British practice for the medical practitioner to recommend such home treatments to his patients. What I wish to suggest is that British Treatment Centres might make it part of their routine to consider the possibilities of this in suitable cases, giving advice as to where the heat should be applied—which would not always be where the patient thought necessary—and how best it could be applied under home conditions.

Methods of massage abroad follow the same principles generally as in our country. At some centres, as will have been noted, there is less use of (though not necessarily less importance attached to) massage than is usual in the best British clinics. The reason for this may be economy. Again referring to "self-help," it would perhaps be possible in certain cases to utilise it to some extent in reducing the number of attendances for massage at clinics. Ignorant massage is, of course, a source of evil, rather than of benefit; but with skilled advice at the outset, professional massage might be supplemented with some simple home massage.

Remedial exercises could certainly be carried on by the patient—again with skilful advice at the outset, and the necessary degree of periodical supervision afterwards—in the home.

In all the simple physical treatments the objective of a Rheumatism Treatment Centre should be education of the patient to do all that is possible in the way of self-help and thus save time at the clinic.

DRUG TREATMENTS.—Foreign observations on the dangers consequent on regarding aspirin and other drugs of the salicylate group as curative instead of merely palliative of symptoms I

have recorded in Section II. These reinforce British medical conclusions on this matter. Since most of the advertised nostrums for the " cure " of rheumatism are compounded chiefly of the salicylate drugs, and since even some medical practitioners are inclined to rely on their use, there should be constantly included in educational literature on the subject of rheumatic disease a warning on this point.

The favourable and unfavourable views in regard to the value of gold injections for the treatment of rheumatoid arthritis have been noted in Section II. The Empire Rheumatism Council has a special clinical research committee (of which I am a member) at work seeking definite conclusions on this matter, and that committee will keep in touch with similar investigations in America (where the weight of opinion at present is generally sceptical as to the value of gold treatment). There is also, it will be observed, controversy among those who have faith in gold as a curative agency regarding the dosage—whether this should be heavy or otherwise.

Until the results of the investigations now being carried out are known, it would be probably the wisest course for Rheumatism Treatment Centres in our country to consider this method of treatment as on trial and not as yet generally accepted. Its use should be restricted to clinics having on their staffs practitioners with experience of its administration.

Prontosil and formulæ allied to it have claimed such dramatic attention recently in the treatment of other diseases that it is natural that they should be tested in the rheumatic group. Reasoning by analogy, it should be very useful in that form of arthritis (gonorrhœal) in which the infective agent is clearly established, and this agent is highly susceptible to chemical therapy. In practice that reasoning apparently has proved sound, and prontosil should be admitted to the armoury of practitioners in dealing with that particular form of rheumatism.

Vaccine Treatments.—The evidence collected abroad in regard to the value of vaccine treatments for rheumatic disease is to a high degree conflicting, as has been noted in Section II. It is, on the whole, unfavourable in regard to stock vaccines; somewhat more favourable as regards autogenous vaccines and specific organism vaccines. This subject has been somewhat fully discussed in the chapter referred to. My conclusions are:

1. That in view of the present lack of ætiological certainty

regarding the causative factors of rheumatic disease, it would not be wise to accept vaccine treatment as a principal practice in Rheumatism Treatment Centres.

2. That at one or more Treatment Centres, properly equipped for the purpose, there should be carried out, under a rigid system of controls, a series of independent tests of vaccine treatments; that this centre or centres should seek to establish close co-ordination with any existing clinics at home or abroad giving special attention to vaccine treatments.

3. That, pending results of this investigation, vaccine treatments should not be discouraged in cases where other methods of treatment have not given good results, but that control records of results in those cases should be obtained as far as that is feasible.

Septic Foci.—The contrasting opinions held by workers in foreign clinics in regard to septic foci in relation to rheumatic disease confirm, I venture to say, the present general view in Great Britain—viz., that they are important, but not so generally or vitally important as was considered by some at one period. In one form of arthritis, the gonorrhœal, where the specific infection is known, they are clearly causative. In other forms the relation is not so clear as to justify a routine extirpation of teeth and tonsils suspected of being septic.

There does not seem to be a case for recommending to British Rheumatism Treatment Centres departure from the present "middle course" taken by the majority of the medical profession; to regard an ascertained focus of infective organisms as something which should be removed, but not holding that there will follow as a certainty the end of the rheumatic infliction, nor neglecting other curative measures.

The Time Factor.—The wide variations of judgment abroad in regard to the term of treatment necessary will be noted, ranging from three weeks (which is common) up to three years. It is clear that these judgments are based far more on economic than on medical considerations; the term is what it is thought can be afforded, not what will effect a cure.

As affecting this treatment time factor, the one clear conclusion is that the best hope is in providing treatment in the early stages. The period of treatment—in the sense of treatment as invalids—would then be *nil* in a very great number of cases. The patient could go on with his or her ordinary avocations.

Where cases have been neglected to the stage at which seriously morbid conditions have been allowed to develop there can be no hard-and-fast limit set. Cure, or such progress towards cure as will make a fairly normal life possible with proper precautions of régime, etc., may be a matter of weeks, months, or years.

British Treatment Centres should therefore base their policy on sedulous endeavour to gather in the early cases, and not attempt to set any time limit to advanced cases. They should be kept under treatment, either in bed or as ambulatory patients, until all that can be done is done for them.

After-care supervision following any period of treatment is most important in this respect. The best system of this I found in the United States. There the social services auxiliary to the Treatment Centres provide the treating physician with pertinent facts beyond what can be elicited by medical examination, and also see that the subsequent course of each case is accurately and sympathetically followed, with a resultant benefit to the patient and an increase in the knowledge of the course of rheumatic disease. It is not only beneficial to the patient's physical condition to have some out-of-hospital help and supervision, but also of great value in sustaining morale.

Spa Treatment.—Spa treatment in Europe is more widely, in America less widely, used than in Great Britain. On the question of its value in the rheumatic diseases I cannot do better than to quote Lord Horder (*International Bulletin*, vol. xxxvi., 1938):

"It is, however, the opinion of most physicians that spa treatment is of definite value in a great number of cases. The psychological effect is frequently remarkable; the patient feels that something definite—something 'sensational,' if I may venture that much-abused word—is being done for him, and in response rallies his own inner resources of healing. Then the change of air, of diet, of régime generally has usually some beneficial effect. All this apart from the degree to which any specific curative effect of the spa waters can reinforce the ordinary course of therapeutic treatment."

That the resources of the excellent British spas are not used as fully as they might be is well known, and negotiations are going on between the British Spa Federation and the British Medical Association to seek practical methods of extending their usefulness in treating the poorer classes of patients. The chief diffi-

culty is the economic one. In a measure that difficulty could be relieved by the establishment, in close neighbourhood to the British spas, of what might be called "occupational and treatment hostels," where patients likely to need prolonged periods of treatment could follow some light gainful industry, agricultural or manufacturing. This would take up some of the burden of their maintenance and make their lives happier.

In conclusion I can only express the earnest hope that there will be gleaned from this report some practical hints for a sound and economical plan of treatment of the rheumatic diseases.

APPENDIX

ITINERARY

The following is a record of the centres I visited and the workers I met. I wish to express my sincere thanks to all these workers for their great assistance.

HOLLAND

June 7 to 15:

Instituut voor Physische Therapie of Amsterdam.
Wilhelmina Gasthuis.
University Hospital of Leyden.
Drs. Van Breemen, Van Dam, Plaat, Professor Snapper and Dr. Touw.

DENMARK

June 16 to July 3:

Bispebjerg Hospital.
Almindelig Hospital.
Finsen Institute.
Skodsborg Sanatorium.
Skaeskorr Gichtsanatarium.
Professor Secher, Drs. Rassmussen, Jarlov, Johannsen, Anderson, Jacobsen.

SWEDEN

July 3 to 10:

Vanforeanstalten Cripples Hospital.
Nynäs Kuranstalt.
Varberg Sanatarium.
Varberg Hospital for Diseases of Bone and Joint.
Drs. Gordh, Sundelin, Edstrom.

GERMANY

July 10 to 25:

Forschungsinstitut für Rheumabekampfung, Berlin.
Hubertus Krankenhaus.
Landesbad, Aachen.
Professor Rother, Drs. Fehlow, Ludwig, Gehlen, Lemmerz.

FRANCE

July 25 *to August* 12:

Aix-les-Bains, Etablissement Thermale.
Reine Hortense Hospital.
Drs. Forestier père et fils, Drs. Françon, Merklen, Certonciny, Graber Duvernay, Saidman, Herbert, de Lavis Trafford, Robert, Tixier and Professor Enselme.

ITALY

August 13 *to* 30:

Termi di Agnano.
Termi di Abano.
Fonte di Fiuggi.

ROUMANIA

BUCHAREST, *August* 31 *to September* 6:

Professor Danielopolu.

HUNGARY

BUDAPEST, *September* 7 *to* 14:

Drs. Pap, de Chatel, Külley, Tölgyes, Charmant.

CZECHO-SLOVAKIA

September 15 *to* 25:

Pistany.
Trencianske Teplice.
Sliac.
Drs. Kollar, Veres, Cmundt, Schmidt, Reichert, Neuwirth, Lenoch.

U.S.A. AND CANADA

NEW YORK, *October* 15 *to November* 3:

Presbyterian Hospital.
New York Hospital.
Belleview Hospital.
Hospital for Chronic Diseases.
Rockefeller Hospital.
Drs. Dawson, Cecil, Swift, Boots, Tyson, Müller, Angevine, McEwen, Dodge, Seegal, Burbank.

BOSTON, *November* 4 *to* 10 *and subsequently :*

Massachusetts General Hospital.
Robert Brigham Hospital.
City Hospital.
Boston Dispensary.
House of the Good Samaritan.
Drs. Bauer, Short, Coggeshall, Swaim, Osgood, Hall, Nissen, Kuhns, Keefer, Pratt, Tannhauser, Duckett Jones.

MONTREAL, *November* 12 *to* 16:

Royal Victoria Hospital.
Dr. Taylor.

TORONTO, *November* 17 *to* 20:
Toronto General Hospital.
Drs. Fletcher, Graham, Gardiner.

PHILADELPHIA, *November* 21 *to* 28:
Abington Memorial Hospital.
Drs. Pemberton, Scull, Bach.

November 30 *to December* 3 *and subsequently :*
Johns Hopkins Hospital, Baltimore.
Marine Hospital.
Drs. Wainwright, Long, Ceder.

MAYO CLINIC, *December* 15 *to January* 8, 1939:
Mayo Clinic.
Drs. Hench, Slocumb, Krusen, Ghormley, Rynearson, O'Leary, Craig, Love, Sacasa, Rosenow.

CHICAGO, *January* 9 *to* 15:
Drs. Irons, Phemister, Hunt, Vrtiak, Kovac, Sideman, Jordan.

PITTSBURG, *January* 16 *to* 20:
Drs. O'Neill Sherman, Ferderber, Margolis.

WASHINGTON, *January* 21 *to* 24:
Billings Hospital.
Walter Reed Hospital.
Drs. Yater, McEnerney, Crain.

NEW HAVEN, *January* 25:
Yale University School of Medicine.
Dr. Paul.

And again to New York and Boston until February 18, 1939.

GOUT AN UNSOLVED PROBLEM

By J. BARNES BURT and R. G. GORDON

At the recent International Conference on Rheumatic Diseases held at Bath a whole day was devoted to the subject of "Gout," but in spite of many interesting papers it must be confessed that no startlingly new contribution to our knowledge of this disease emerged from the discussion.

There is no reason to doubt that gout is essentially a disease of metabolism, but in spite of the recent major advances in biochemistry the only real progress that has been made in this direction is an improvement in the accuracy of tests which are supposedly useful in the diagnosis of the disease. Modern tests for uric acid in the blood are far superior to Garrod's thread test, but the increased accuracy of such tests is not so valuable as it might be, since it would appear that in the opinion of most authorities a low blood uric acid content is not inconsistent with a diagnosis of gout. A great deal of work has been carried out in estimating the sedimentation rate, leucocytosis, and the Cooke-Arneth's blood count in gout, but the observations proved to be of no help in diagnosis, for, in fact, most of such work emphasises points of resemblance between gout and rheumatoid arthritis rather than points of difference between it and other forms of arthritis. Considering the great advances in medicine in the twentieth century it is curious that our knowledge of a disease described by Hippocrates, Sydenham, and Garrod is still so chaotic, and a candid discussion on some peculiar features of gout ought to prove instructive.

1. Heredity

Practically all authorities, with the exception of Freund (1938), agree that heredity is a very important factor. The following table shows the estimate of five experienced observers:

HEREDITY IN GOUT

Author.	*Per Cent.*	*Remarks.*
Duckworth, D.	50–75	—
Garrod, A.	50	Hospital patients.
Garrod, A.	75	Private patients.
Hill, L.	45	Chiefly hospital patients.
Luff	81·3	Private cases only.
Osler	50–60	—

When one considers that gout may lie latent for a generation, and that parents may have died at an early age before gout showed itself, these figures are most impressive and almost justify Llewellyn's (1920) statement that an heredity factor is invariably present.

On the other hand, Freund (1938) considers that similarity of environment and similar habits and methods of living have led to the tradition that gout is hereditary. In the writers' opinion this is not a sound argument, for while our grandfathers may have been three- or four-bottle men, later generations are far more moderate in eating and drinking and probably take much more exercise to a later stage of life.

It is not uncommon to find a history of the so-called allergic diseases—eczema, asthma, hay fever and urticaria—in the relations of those suffering from true gout, which not only suggests an allergic factor in the production of gout, but also the presence of an hereditable diathesis such as is suggested especially by the French school.

As a matter of fact, it is difficult to find any record of exact work in recent literature. Hamilton (1900) says: "The conclusion I have arrived at is that the gouty habit of body has arisen as a variation, and as such is hereditarily transmissible, and that excess of diet and alcohol merely renders the habit of body apparent."

Thomson (1908) says: "All that can be said at present is that the predisposition to gout is an inborn character which, like any other, may be transmitted. Even if gout turns out to be definitely microbic, the general argument will not be seriously affected."

Baur, Fischer and Lenz (1931) say: "The inheritance of gout is as a rule a simple dominant. In many families the gouty

diathesis can be traced through several generations, in other families the course of the heredity appears to be interrupted, this, perhaps, being because external influences (and especially the nature of the food) are of great importance as exciting causes of attacks of gout."

On the other hand, they remark that "gout may be included in the group of the idiosyncrasies or allergies. These are all characterised by a morbid susceptibility to substances which are harmless to normal individuals. Gout is an idiosyncrasy towards nucleoproteins of animal origin. There are many such morbid idiosyncrasies. B. N. Belaieff has described an hereditary idiosyncrasy towards egg albumin. We are indebted to Hanhart of Zurich for the sight of a number of interesting family trees compiled by him showing idiosyncrasies as the outcome of which allergic reactions could be induced by various substances in different members of the same family. The heredity appears to be dominant."

In gout, therefore, there would appear to be at least two hereditable factors, both of which require to be present, together with certain environmental influences, in order to determine the manifestations of the disease:

(1) A sensitiveness to certain articles of diet or certain products of metabolism.

(2) A tendency to store uric acid in the body, and to precipitate biurate crystals in certain tissues.

2. Attacks produced by Specific Articles of Diet

It is well recognised that in certain gouty people small quantities of such things as cider, asparagus, rhubarb and strawberries can produce typical attacks of gout, and that the same thing does not necessarily produce an attack in different people. This phenomenon is as definite and rapid as the production of urticaria by shellfish in susceptible persons; in fact, the phenomenon resembles in every respect a true allergic reaction. Where the "antigen" or equivalent sensitising substance—cider, for instance—is not recognised, and the cider continues to be taken, a serious condition is set up in the affected joint and a traumatic element is introduced as a result of frequent use of an inflamed joint, which leads as a sequela to thickening of the synovial membrane, damage to the cartilage and changes in

the bone. It is important to differentiate between the " attack " and the sequelæ of such an attack or attacks. Occasionally the reaction appears to be due to a summation of stimuli. One of us had a case who could take ham or beer separately with impunity, but if he had a lunch consisting of a plate of ham and a glass of beer he invariably got an attack of gout.

It is a possibility that lead may produce gout in the same way as cider, etc., but the curious geographical distribution of saturnine gout suggests that lead will not produce gout except in localities where gout is prevalent.

SATURNINE GOUT

Author.	*Number of Cases of Gout.*	*Percentage of Saturnine Gout.*	*Remarks.*
Duckworth, D. ..	136	18·0	St. Bartholomew's Hospital.
Garrod, A. ..	(?)	35·0	St. Bartholomew's Hospital.
Lancereaux ..	24	33·0	Paris (in saturnine nephritis).
Lindsay	482	22·8	Mineral Water Hospital, Bath.
Pye Smith ..	61	3·5	Guy's Hospital.

On the other hand, in Freich's clinic in Berlin, out of 163 cases of lead poisoning there were no cases of gout. In Newcastle, where there are a large number of cases of lead impregnation, gout is not seen in association with that condition. In Glasgow, Edinburgh and Dublin the physicians state that gout in association with lead is unknown.

It is not only manual labourers who suffer from saturnine gout; certain very severe cases of gout among the upper classes have been due to a slightly excessive proportion of lead in the drinking water. Van Breemen quotes a case. A well-to-do Englishman living in one of the eastern counties consulted him on account of severe and frequent attacks of acute gout. The patient was put on a strict régime, but at the end of two months showed no improvement. Van Breemen then went into the question of the water supply, and the sample sent to Utrecht proved to contain a somewhat excessive amount of lead. The fault in the water supply was therefore corrected, and for the next two or three years the patient had no attacks of gout. Some three years after the original consultation the patient

stayed at a large hotel in the West of England, and this visit was followed by a severe attack of gout. The patient communicated with Dr. Van Breemen, and the water supply of the hotel was tested and found to contain an excessive quantity of lead.

There are many peculiarities about the action of alcohol in producing an attack of gout; for instance, beer will bring on an attack in one man who can take champagne with impunity, while other men can take beer and not champagne. Most gouty subjects get mild twinges after taking port, but reasonable quantities of whisky seldom produce gout. Certain physicians explain the action of alcohol by its action on the liver, but if this were so why should the small quantity of alcohol in port be so much more deadly than a large amount of alcohol in whisky? Would it not be more reasonable to say that the gouty patient is allergic to certain constituents associated with alcoholic beverages, just as the hay-fever patient may be allergic to pollen from Timothy grass and not to that of other forms of grass?

An analogous susceptibility of tissues to different alcoholic beverages was pointed out by Ritchie Russell in connection with a case of myotonia, who had found that his muscles were sufficiently released to enable him to dance through a whole evening if he consumed a pint of a certain kind of ale, but it was impossible to reproduce this effect with any other form of alcohol from "absolute" downwards.

It is a curious fact, so far unexplained, that if we assume that the susceptibility to foodstuffs producing such a specific effect as an acute attack of gout is an hereditable variant, the food substances vary to such an extent.

So far as we have been able to ascertain no investigation has been carried out as to whether gouty subjects deriving from a gouty ancestor are susceptible to the same foodstuffs, but clearly this is a proposition which might well be proved or disproved.

An argument in favour of the allergic nature of the acute attack of gout is its sudden onset and sudden relief.

This points to the reaction being an antigen-antibody reaction. If, as has been suggested, a low-grade infective arthritis or even an actual necrosis of tissue precedes the deposits of biurate crystals, it is difficult to understand the complete remission and rapid relief in cases of gout, for in favourable cases—

that is to say, those in which the acute attack is not too prolonged or is not repeated too frequently—there may be no obvious residual affection of the joint.

It is only in the stage of acute attacks that the administration of the time-honoured specific colchicum is most useful. Its pharmacological action is up to the present a mystery, since all its proved actions on the body can be brought about more potently by other agencies, but these latter do not have a specific action on gout.

In the consideration of gout it is important to recognise two definite stages: (*a*) the initial acute onset which so closely resembles an allergic attack, (*b*) the effect on the joints of repeated attacks. The deposition of crystals of biurate interferes with the smooth action of the joint and introduces an element of trauma, and in the case of a long attack or repeated attacks of gout a condition which started as gout ends by becoming a chronic traumatic arthritis, which latter condition is not benefited appreciably by colchicum and requires quite different treatment, largely by physical measures, which may be strongly contra-indicated in the acute allergic stage. The general symptoms—fever, mental irritability and depression—do not negative the suggestion that the attack is allergic, while the rapid sedimentation rate, the leucocytosis, and the shift of the polynuclear count may all be found in certain phases of allergic conditions. It may be noted, however, that there is no eosinophilia in gout.

It must be admitted, however, that the above phenomena are more common in cases of infection than in cases of allergy, and some observers have suggested that gout has an infective rather than an allergic origin. Llewellyn (1920) definitely puts forward the suggestion that the "latent tissue peculiarities of the gouty through the agency of infections become manifest as gout, and that the said organisms excite the inflammatory reaction with sequential uratic deposition."

But the onset of an acute attack of gout as a direct result of two glasses of port or a large tumbler of cider is a strong argument against the infective theory, as is also the fact that complete remission occurs in spite of the focus of infection being untreated. Again, in many cases freedom from attacks of gout follows a strict dietetic régime, although this strict régime cannot possibly affect the septic tooth, the septic tonsil or infected

sinus. Everyone admits that the removal of a septic focus may be of great value in the treatment of gout. Many other diseases benefit in a similar manner. This does not prove that the septic focus is the cause of the disease; it may be an additional burden, which when removed enables the body to tackle successfully certain abnormalities.

In view of the importance of vitamins in metabolism, particularly the action of vitamin B_1 in the oxidation of carbohydrate and perhaps lactic acid, the recent work of Vorhaus and Kramer (1938) is interesting. They record twenty-five cases of gout treated with thiamin chloride (vitamin B_1). The most striking observation as the result of this administration was the flare-up of the symptoms and signs, but, as they remark, additional observations by other workers are necessary to prove a relationship between gout and vitamin B_1.

There is no question, as Thomson (1938) has pointed out, that derangement of the liver is traditional in gouty subjects. As we have already stated, the explanation that the liver cannot deal adequately with alcohol lacks proof, and it may be that one factor in gout is the deficiency of some essential substance, hormonic or otherwise, in the liver, or more generally, in the reticulo-endothelial system. It is interesting to note that Barker and Oriel (1928) have shown that just before and during an allergic attack they found a positive Van den Bergh reaction of the biphasic type in a large proportion of cases. They believe that these changes are indications of a disturbance of hepatic function.

This leads us to consider the peculiar phenomena associated with error in purine metabolism, which, as has been said, may be an hereditable variant.

All mammals, with the exception of man, are able to destroy uric acid rapidly. This destruction is caused by uricase, a ferment found in the liver, kidneys and muscles, except in man, and curiously enough in Dalmatian dogs. In birds, ammonia and lactic acid are synthesised in the liver to form uric acid, but this does not occur in mammals. The only condition analogous to gout in mammals is found in swine, who get deposits of guanine in muscles.

Umber (1910) and his pupils have proved that the excretion of uric acid is delayed in a gouty subject. This has been confirmed by Vogt, Walker Hall and several other observers. Osler

(1912) states that the slow elimination of uric acid is the most important factor in gout.

Folin (1923), on the other hand, has demonstrated that uric acid injected into gouty patients is excreted as rapidly and completely as in normal controls, and there is ample evidence that in the earlier stages, at least, gouty persons can concentrate uric acid in the urine to as high a level as normal individuals. It would seem, therefore, that the kidney is not at fault, but that there is a tendency to store a substance in the tissues which is a perfectly normal product of metabolism. We may detect here a certain analogy to diabetes. Are we therefore to suppose that some hormone is absent or deficient in gouty persons, as insulin is absent or deficient in diabetes, or perhaps that some enzyme like hæmopoietin is absent as in pernicious anæmia? There is as yet no answer to this question, but it is a point which might indicate a future line of research. Help might be obtained by a further study of the condition in which the levels of uric acid in the blood reach a maximum—namely, leucæmia, a disease of the liver-bone marrow relationship which we now describe as the reticulo-endothelial system. Leucæmics do not suffer from gout, but that is evidently because they do not possess the susceptibility to certain foodstuffs nor the tendency to the deposition of urates, which are presumed to be hereditable variants in gout.

All the above facts fail to explain, however, a sudden deposition of uratic crystals which follows two glasses of port wine or a tumblerful of cider, nor do they explain the rapid and complete absorption of these; and it will be instructive to consider the possibility of explaining the rôle of uric acid in gout from an entirely different standpoint—namely, that uric acid is the result of an attack of gout, and not the cause. This is suggested by Llewellyn (1920) and is the thesis of Matthieu Pierre Weil (1938). It should be noted that in early cases of gout there is no excess of uric acid in the blood, excepting during the attack. Daniel relates two cases where acute attacks of gout occurred when the blood uric acid was at a subnormal level, the victims being at the time on atophan. The continuous excess is only found after long-continued attacks or when attacks are frequent; therefore a low blood uric acid during a remission does not mean that a given attack of acute pain in a joint cannot be gout.

An interesting point in relation to the acute attack of gout is the frequency of attacks in early spring and late autumn. It is difficult to find an explanation of this phenomenon; the only other group of diseases showing this seasonable attack is the infectious group—measles, scarlet fever and diphtheria, and also rheumatic fever (Rowlands, 1938). Two possibilities occur to the mind: firstly, that seasonable foodstuffs such as rhubarb may be a factor; or it may be a sensitivity of the organism to climatic changes—from summer conditions to winter and again from winter to summer. That climatic conditions do influence the organism is obvious, but the exact nature of the influence is not easy to explain.

In a man between the ages of thirty and forty, who suffers from an acute attack lasting only a few days, the uric acid in the joint is probably absorbed rapidly by the blood, and Dyce Duckworth (1889) relates a case in which at post-mortem no traces of biurate crystals were found in the big toe of a man of forty-three after two acute attacks of gout in that joint. Where the attack occurs in older men, and lasts from ten days to three weeks, the amount of uric acid deposited is too great to be absorbed rapidly, and the resulting damage to the joint produced by the crystals predisposes that joint to another attack of gout. It is by encouraging the excretion of uric acid in the intervals between the attacks and thus freeing the joints that cinchophen proves useful. It is well recognised that cinchophen fails to relieve an acute attack of gout. Many have seen and described patients who, starting with typical attacks of gout with complete remission, gradually, with the increase of age, or some lowering disease, such as gastric ulcer, develop a chronic arthritic condition closely resembling rheumatoid arthritis. This fact suggests that the patient with a lower vitality is unable to react to the antigen, whatever it is, with the result that the joint condition fails to clear up.

Weil's suggestion with regard to the deposit of crystals is that the allergic reaction produces an acute response in and about the joint, with an intense concentration of leucocytes in the neighbourhood. Just as in the case of leucæmia, therefore, there is an intense production and intense destruction of leucocytes, with resultant liberation of uric acid. Since, in gout, this is a local rather than a general process, there is a local deposit of uric acid in the form of biurate crystals and at the same time

an absorption into the blood stream which, owing to the supposedly inherent error in purine metabolism, cannot be dealt with efficiently, and so uric acid gradually accumulates. But we should remember that these conditions of concentration of leucocytes hold in any suppurative condition where the leucocyte exudation and destruction are far more intense than in gout, and even in gouty subjects there is no evidence that biurates are deposited in the neighbourhood of septic foci.

Tophi tend to be deposited in somewhat avascular tissues—namely, in cartilage, synovial membrane in joints or bursæ, and in the medulla of bones. In certain advanced cases of gout deposits of biurates have been found in the papillæ of the kidneys (sixteen out of eighty—N. Moore).

In advanced kidney disease neither uric acid nor urea is excreted in normal quantities, and a high content of uric acid in the blood occurs in kidney disease without a necessary association with gout. This indicates that renal defect is not a cause of gout.

All textbooks state that chronic nephritis is a common sequence of gout. In our experience this is rare. In Hill's (1938) figures only nine cases out of a total of ninety-three cases of gout had serious renal inefficiency. It is to be remembered that alcohol, excessive meat intake and lead predispose not only to gout, but to arterio-sclerosis, and it is quite likely that in those cases of gout which develop nephritis the nephritis is due, not to the gout, but to the alcohol, etc., which have also been responsible for the gout.

3. Clinical Features of Gout

There is a tendency nowadays to restrict the diagnosis of gout to those cases in which there is a clear history of a typical acute attack or in which tophi can be demonstrated.

Furthermore, there is a widely-held belief that gout is found almost exclusively in men. That it is much commoner in men than in women none will deny, and the fact that men are more subject to trauma, especially in the big toe, that they indulge more freely in alcohol, and that some of them are exposed to lead and other metallic poisons may be a partial explanation. In the much-quoted aphorisms of Hippocrates we learn that eunuchs are immune to gout, whilst in females gout is usually

delayed until after the menopause. If these statements were true we should have to look for an endocrine factor in the causation of gout. However, Galen states that eunuchs in his day readily begat the disorder, and Seneca, writing of the decadent period of the Roman Empire, states that women rivalled men in their bodily disorders. Nevertheless, frank gout is less uncommon in women, especially after the climacteric, than is generally supposed, and the following two cases occurring in women under forty show that it can and does occur in younger women:

E. B. (charwoman, aged thirty-six) suffered from gout for the last five years. The first attack was in the right big toe, and most of the joints have been affected at one time or another. The father suffered from stone in the bladder, but there was no family history of gout; there was, however, a history of large excess of alcohol. When the patient was first examined she was suffering from a severe attack of gout in the knees, feet and left wrist. There was a deposit of urates in the right olecranon bursa and around the terminal joint of the middle finger of the left hand; no tophi were present in the ears. A skiagram of the left hand showed a transparent area about the size of a pea in the distal end of the second phalanx of the middle finger (Burt, 1908).

D. B. (a trained nurse, aged thirty-two years). Admitted to the Royal Devonshire Hospital, Buxton, in June, 1927. She gave a history of pain and swelling in the small joints of the hands and feet intermittently for nine years. The onset of the first attack was sudden. On examination the right knee was hot and swollen, and both big toes swollen and tender; there was a tophus in the right ear; blood uric acid (Benedict direct) was 7·95 mgm. per cent. The urine contained a trace of albumin, and hyaline and granular casts were present.

Apart from this, however, it is possible that gout may sometimes appear in men, and more particularly in women, in a less spectacular form than that generally described, and thus escape diagnosis. No doubt some cases diagnosed as rheumatoid arthritis in women are of a gouty nature, and Mallory (1910) has shown that 47·3 cases of rheumatoid arthritis in women show a prolongation of the period of exogenous uric acid excretion, and two cases showed increased uric acid excretion during subacute attacks of arthritis. This question requires careful revision. At present probably most physicians would say that

the differential diagnosis of rheumatoid arthritis and gout presents no difficulties, but we are by no means certain of the truth of such an assertion.

In the young, robust man the violence of the reaction in gout is a marked feature; in fact, no other disease shows such a violent reaction, and it is this reaction which leads to the rapid and complete remission. As the reactions grow milder, a not infrequent condition with the increase of age or lack of vitality, gout takes on a chronic form and may simulate rheumatoid arthritis. In so-called rheumatic gout the thickening of synovial membrane, stiffening and swelling of the small joints without the profound trophic changes characteristic of rheumatoid arthritis, so frequent in the female descendants of gouty men, is possibly an attenuated form of true gout, in which the reaction is too mild to neutralise the antigen, with the resulting development of what is really a chronic traumatic arthritis. Of course, it is possible that a joint damaged by gout is predisposed to infection, and no doubt there are joint lesions the proper diagnosis of which would be infective arthritis superimposed upon gout. In common with other articular tissues subject to the continued offensive of noxious influences, these joints may eventually develop degenerative changes and clinically become diagnosable as typical osteo-arthritic joints. We believe that such an outcome of chronic gout is relatively common.

It is interesting to compare this sequence with that met with in asthma. In the earlier stages the attacks of asthma are apt to clear up, leaving no complications behind, but after several years of asthmatic attacks, particularly if these are frequent, organic changes develop, such as bronchial catarrh, fibrotic changes around the tubes and emphysema. Often the condition is complicated by infection of the bronchi, and the same phenomena may occur in a chronic gouty joint.

Again, intermittent hydrarthrosis is by many considered an allergic phenomenon. In this condition, at first there are complete remissions; gradually, however, organic changes occur, and a chronic arthritis is the result.

Similarly, the arthritis following injections of horse serum is undoubtedly allergic. The condition generally clears up in a few days, but not always. Two nurses have recently been admitted to the Royal National Hospital for Rheumatic Diseases at Bath in whom a mild chronic arthritis followed directly

in one case antidiphtheric serum and in the other antistreptococcic serum. The arthritis had lasted for months before they were admitted to the hospital, and was not completely cured after six weeks' treatment.

It must be admitted, however, that from the clinical point of view the attacks of serum arthritis in no way resemble attacks of acute gout. Pain, when present, is due to stretching of the capsule, and not to acute inflammation, and there is no redness, heat or œdema.

Fibrositis

It is noteworthy that in almost every case of gout an associated fibrositis may be found. In the nineteenth century the chief authorities on gout all mention it as a cause of fibrositis. For instance, Garrod (1876) states that gout affecting the muscular system appears to be of the same nature as true gouty inflammation. Duckworth (1889) states that muscular rheumatism is really gouty, and says that uric acid deposits have been found in muscles. This must be very rare, for no other observer has described uric acid in muscles, and the absence of synovial fluid and cartilage and the excellent blood supply make such deposit unlikely.

Llewellyn (1920) states that clinically one meets with all forms of fibrositis in association with acute articular gout. In spite of this, the medical profession is slow in acknowledging a true gouty fibrositis. We have seen attacks of fibrositis in gouty subjects every bit as sudden in their onset as acute attacks in the big toe. Stiffness and pain in the shoulder muscles is a common sequence to over-eating and over-drinking, and, indeed, success often attends treatment identical with that which would be employed in a case of frank gout, including the exhibition of colchicum.

We may therefore have to revert to the ideas of our ancestors to some extent and be less diffident in the employment of the adjective " gouty."

In any case, it is clear that this disease is a reproach to medical science, and that we know little more about it—perhaps clinically not so much—than did our ancestors.

Summary and Conclusions

1. Although there have been considerable improvements in, and additions to, the biochemical tests available in the diagnosis of gout, the tendency has been for the differential diagnosis of certain aspects of the disease from other forms of arthritis, especially rheumatoid arthritis, to be *more* rather than less difficult.

2. The evidence in favour of heredity is overwhelming, even if all cases not showing classical symptoms are excluded. It seems probable that there are at least two heritable factors, but these will only manifest themselves if certain environmental influences are present. These factors are:

1. A sensitiveness to certain articles of diet or certain products of metabolism.
2. A tendency to store uric acid in the body and to precipitate biurate crystals in certain tissues.

3. The attack of gout which should be distinguished from the sequelæ of such an attack or attacks is a typical allergic reaction.

4. Lead absorbed into the tissues may act as a precipitant of an attack, but in the absence of other factors does not cause gout.

5. The delay in excretion of uric acid may be due to the absence of some hormone, as in diabetes, or some enzyme, as in pernicious anæmia, and the factor determining this may be inborn or acquired.

6. The deposition of uratic crystals may be a result rather than a cause of the " attack."

7. Gout is found less exclusively in men than is generally supposed, and certain cases of chronic arthritis, and perhaps of fibrositis, not usually classified as gout, ought to be included in this category.

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THE EFFECT OF CHRYSOTHERAPY ON THE SEDIMENTATION RATE IN RHEUMATOID ARTHRITIS

By WILLIAM GOLDIE*

Introduction

In a disease such as rheumatoid arthritis the assessment of the results of any form of treatment is admittedly a matter of great difficulty. It is now generally accepted, however, that the blood sedimentation rate (B.S.R.) is an accurate index of the activity of the disease at any stage, and that any lasting improvement in the condition will be accompanied by a fall in the B.S.R. More and more reliance is being placed on this test to corroborate the clinical result of different kinds of therapy. For this reason it is a pity that in only a small proportion of the many papers which have appeared in the past few years on the gold treatment of rheumatoid arthritis has an attempt been made to assess the effect of this form of treatment on the B.S.R.

A fall in the B.S.R., in the majority of cases as a result of chrysotherapy, has been reported by Hartfall, Garland and Goldie (1937, 1938); by Parr and Shipton (1937); and by Copeman and Tegner (1937). The latter reported a preliminary rise in a small proportion of cases, and a subsequent fall; in certain patients, too, a preliminary fall was succeeded by a permanent increase in the B.S.R., and it was suggested that some degree of tolerance to gold therapy might be established. Forestier and Certonciny (1936) concluded, from a study of fifty cases, that a gradual fall in the B.S.R. was a favourable prognostic sign, whereas a stationary or increasing rate was unfavourable; clinical improvement was usually proportional to the fall in the B.S.R.

Saskin and Spanbock (1937) have studied the behaviour of the B.S.R. in twenty-two gold-treated cases of rheumatoid arthritis. In twelve instances where marked improvement was found the average B.S.R. was 47 mm. before treatment and 11 mm.

* Working with the aid of an expenses grant from the Medical Research Council.

after treatment. In ten cases where no improvement resulted the average B.S.R. was 49 mm. before treatment and 48 mm. after.

More recently Ellman and Lawrence (1938) have reported in detail on the change in the B.S.R. in a series of twenty control and forty gold-treated cases of rheumatoid arthritis, all of which received some form of physiotherapy. The B.S.R. became normal in twenty-two of the gold-treated and in five of the control cases. The conclusion reached by the authors was that physiotherapy produced no definite change in the B.S.R., whereas chrysotherapy caused a slowing of the rate. They appear to imply, therefore, that the B.S.R. will become normal in a proportion of cases without treatment.

The purpose of this paper is to discuss the effect of chrysotherapy on the B.S.R. in a series of 400 cases of rheumatoid arthritis selected from the files of the arthritis clinic of the Leeds Public Dispensary and Hospital. These cases have been under observation over a period varying from six months to four years, and have been included in previous publications (Hartfall and Garland, 1935, 1936; and Hartfall, Garland and Goldie, 1937, 1938). The following criteria have been used in their selection:

(1) The cases conform to the criteria proposed for the diagnosis of rheumatoid arthritis in the British Medical Association classification (1933). Although no attempt has been made to differentiate " primary " from " secondary " types, the majority fall into the primary group.

(2) Chrysotherapy has been the only form of treatment emplcyed, and cases have not had any previous gold treatment before coming under observation.

(3) Each case has completed one course of treatment and has been observed afterwards for a period of at least three months.

(4) Estimation of the B.S.R. has been carried out before treatment and at the end of each course.

The gold salts employed have been lopion, parmanil, solganal B, oleosum, myocrisin and crisalbine. No attempt will be made in this paper to differentiate between the effects on the B.S.R. of the individual preparations used; it is felt that the results observed were common to all gold salts, and any differences which may exist are so slight as not to affect the main argument.

Of the 400 cases, 116 had one course only, 154 had two, 77 had three, 42 had four, 8 had five, and 3 had six. No adequate

control series has been observed, but it may be stated that an attempt to overcome this defect by injecting a series of patients with sterile saline instead of gold salts had to be abandoned on humanitarian grounds owing to the uniformly bad results.

Clinical Data, etc.

Of the 400 cases, 308 were females and 92 males. Table I. shows the age distribution at the onset of arthritis and at the beginning of treatment.

Table I.—Age Distribution of Cases

Age.	*At Onset of Arthritis.*		*At Beginning of Treatment.*	
	Number.	*Per Cent.*	*Number.*	*Per Cent.*
20 and under ..	18	4·5	4	1·0
21–30	66	16·5	28	7·0
31–40	108	27·0	78	19·5
41–50	115	28·75	101	25·25
51–60	74	18·5	129	32·25
61–70	17	4·25	56	14·0
71 and upwards ..	2	0·5	4	1·0
Total	400	100·0	400	100·0

It will be seen that the onset of the disease occurred under the age of forty in approximately half the cases. It has always been our experience at this clinic that rheumatoid arthritis is rather more frequently found in persons over forty than below this age.

Method.—The Westergren method has been used throughout in estimating the B.S.R. The disadvantages of this method have been discussed recently by Gibson (1938), who concludes that inaccuracies may occur in 5 to 10 per cent. of cases. This test has been found most convenient, however, especially in view of the large number of cases presenting themselves at the clinic each week. For the latter reason, too, no attempt has been made to correct the B.S.R. for any anæmia that may have been present; but as all cases showing clinical signs of anæmia were investigated from this point of view, and chrysotherapy commenced only when the blood count had become normal, it is probable that any error on this account will be negligible. Another possible source of error lies in the fact that in estimating the B.S.R. attention was not paid to such disturbing factors

as upper respiratory infections, menstruation, etc. The large number of cases examined, however, will tend to minimise any fallacies due to these.

The figure used as index of the B.S.R. in this paper is the average hourly reading. Thus, if S_1 be the first-hour reading and S_2 the reading at the end of the second hour, then the average hourly reading (S) is obtained from the equation:

$$S = \frac{S_1 + \frac{S_2}{2}}{2}.$$

In the majority of cases the average hourly reading approximates to the reading at the end of the first hour, as the fall in the second hour is about twice that in the first. In certain cases, however, where there is a lag in the first hour followed by a marked fall in the second hour, the average hourly reading appears to be a much fairer index and to overcome to a certain extent what is the principal disadvantage of the Westergren method—namely, the occasional initial delay in the sedimentation of erythrocytes. At the same time, the best way of expressing the B.S.R. as determined by the Westergren technique is to give both the first-hour and the second-hour readings, but for the purposes of this paper such a method is impracticable.

Results

In Table II. the range of B.S.R. in the 400 cases is shown before and after treatment.

Table II.—B.S.R. before and after Treatment

B.S.R.	*Before Treatment.*		*After Treatment.*	
	Number of Cases.	*Per Cent.*	*Number of Cases.*	*Per Cent.*
0–10	44	11·0	164	41·0
11–20	99	24·75	134	33·5
21–30	85	21·25	57	14·25
31–40	64	16·0	26	6·5
41–50	43	10·75	7	1·75
51–60	26	6·5	6	1·5
61–70	15	3·75	2	0·5
71–80	12	3·0	3	0·75
81–90	7	1·75	1	0·25
91–100	5	1·25	—	—
Total	400	100·0	400	100·0

It will be seen from this table that 11 per cent. of the cases had an original B.S.R. of 10 or less before treatment. This agrees with the experience of Forestier and Certonciny (1936), who find that approximately 10 per cent. of all cases of rheumatoid arthritis have an approximately normal B.S.R. It is obvious from this table that gold therapy causes a marked slowing in the rate. Actually 36 per cent. of cases had a B.S.R. of 20 mm. or less before treatment as compared with 76 per cent. after treatment. If the B.S.R. gives an indication of the activity of the disease, gold treatment appears to slow down its activity or to arrest it altogether. These results, of course, are entirely in keeping with clinical findings, and afford further evidence of the value of this therapy.

It seems to be very important to find out at what stage this slowing takes place, and whether it is maintained in those cases observed over a long period. In Table III. the average B.S.R. before and after each course has been arranged according to the number of courses given.

TABLE III.—TABLE SHOWING AVERAGE B.S.R. AT END OF EACH COURSE GROUPED ACCORDING TO THE NUMBER OF COURSES GIVEN

Number of Courses.	*Number of Cases.*	*Average Initial B.S.R.*	*After First Course.*	*After Second Course.*	*After Third Course.*	*After Fourth Course.*	*After Fifth Course.*	*After Sixth Course.*
1 only ..	116	27·8	14·6	—	—	—	—	—
2 „ ..	154	30·8	15·1	14·9	—	—	—	—
3 „ ..	77	33·8	18·1	14·8	16·9	—	—	—
4 „ ..	42	37·1	19·0	22·4	17·0	20·5	—	—
5 „ ..	8	44·5	20·0	12·0	21·0	21·0	27·1	—
6 „ ..	3	39·0	22·0	43·0	26·0	39·0	28·0	23·0
Total ..	400	31·5	16·1	16·2	18·0	21·6	27·3	23·0

This table shows that the total average fall which takes place in the B.S.R. is entirely determined by the fall taking place at the end of the first course; there is no indication of any further reduction following subsequent courses. It is obvious, therefore, that the fall in the B.S.R. is quite independent of the number of courses given. This finding is surprising, and seems to be at variance with the clinical findings; as a general rule, the clinical improvement which takes place after the second and subsequent courses, though not so dramatic as that after the first, is nevertheless considerable; it has been previously

pointed out (Hartfall, Garland and Goldie, 1937) that results are better with multiple courses.

The explanation of this anomaly may be that the complete or partial arrest of the disease precedes by a considerable interval the abatement of clinical symptoms. It is only to be expected that patients will be left with pain and stiffness after the infective process has been arrested, especially when one considers the destruction of cartilage and replacement fibrosis which the disease leaves in its wake; this point emphasises more strongly than ever the importance of early treatment in rheumatoid arthritis.

In order to learn to what extent the B.S.R. is of prognostic significance in gold-treated cases of rheumatoid arthritis, some statistical analysis of the inter-relationships existing between the following factors has been carried out—viz., initial and final B.S.R., change in B.S.R., disability and clinical result. In a previous paper (Hartfall, Garland and Goldie, 1937) an attempt was made to classify cases into seven grades of disability, and the criteria laid down at that time have again been applied. Briefly, the seven grades represented increasing degrees of disablement varying from Grade 1, where the patient is still able to work, up to Grade 7, where the patient is completely bedridden. In order to save space, only those tables where a definite statistical relationship has been shown to exist will be published.

No association has been found to exist between the initial B.S.R. and clinical result, between initial disability and change in B.S.R., between disability and result, and between initial and final B.S.R. It thus appears that the chances of improvement are equal in slightly and severely disabled cases and in cases with high and low initial B.S.R.s. On the other hand, a significant association has been found to exist between disability and initial B.S.R., between clinical result and change in B.S.R., between final result and final B.S.R., and between initial B.S.R. and change in B.S.R.

The relationship between disability and initial B.S.R. is shown in Table IV. A slight but definite association has been shown to be present, cases in the higher grades of disability tending to show a higher B.S.R. That the association is only slight is to be expected. It would be unlikely that a large series of cases such as this would not include a number of cases where the activity of the disease was becoming arrested, but where marked

disability was left; conversely, patients with a short history and slight or moderate disability have often a high B.S.R. It is surprising, incidentally, how often one finds a high B.S.R. in apparently " burnt out " cases.

TABLE IV.—RELATIONSHIP BETWEEN INITIAL B.S.R. AND DISABILITY

Grade of Disability.	0–10.	11–20.	21–30.	31–40.	41–50.	51–60.	61–70.	71–80.	81–90.	91–100.	*Average.*	*Total.*
1	4	7	1	—	—	1	1	—	—	—	20·0	14
2	21	49	41	25	11	8	5	7	1	3	29·0	171
3	5	12	16	8	3	—	3	1	2	—	29·5	50
4	2	11	5	13	5	5	1	—	1	—	33·6	43
5	8	8	10	10	12	5	4	1	—	1	36·0	59
6	4	11	11	6	12	7	1	3	3	1	36·9	59
7	—	1	1	2	—	—	—	—	—	—	29·0	4
Total ..	44	99	85	64	43	26	15	12	7	5	31·5	400

Correlation coefficient +0·1781.

The relationship between clinical result and change in the B.S.R. is shown in Table V. The classification of the clinical results is the same as was made in a previous publication (Hartfall, Garland and Goldie, 1937).

TABLE V.—RELATIONSHIP BETWEEN CLINICAL RESULT AND CHANGE IN B.S.R.

Clinical Result.	*Change in B.S.R.*									*Average Change.*	*Total.*
	Minus.					*Plus.*					
	81 100	61 80	41 60	21 40	1 20	0 19	20 39	40 59	60 79		
Cured ..	2	1	1	10	15	1	—	—	—	−24·3	30
Markedly improved	1	9	24	57	136	42	5	1	—	−16·4	275
Moderately improved	—	2	5	9	17	8	1	—	—	−16·6	42
Slightly improved ..	—	—	—	1	7	8	1	—	—	−0·6	17
No improvement	—	—	4	4	13	12	1	1	1	−5·7	36
Total ..	3	12	34	81	188	71	8	2	1	−15·4	400

Correlation coefficient +0·2180.

A significant statistical association has been shown to exist between the factors, those cases with better results tending to show a greater fall in the B.S.R. The association is, however, not a very close one; it will be seen that a small proportion of the " markedly improved " cases show a rise in the B.S.R., and conversely a fall in the B.S.R. was observed in over half the cases who did not improve at all. The reason for such anomalous results is not at all clear. It is difficult, however, to rule out altogether the possibility that the improvement in some instances may be entirely psychological; the view has previously been stated that psychogenic factors play no part in the majority of rheumatoid arthritis cases (Hartfall, Garland and Goldie, 1937), but the psychological effect of injection therapy, together with contact with a group of cases showing undoubted improvement, may well explain a stationary or raised B.S.R. in a minority of patients who pronounce themselves " better." It is unlikely that minor intercurrent upsets such as upper respiratory infections or menstruation could be the sole cause of the raised B.S.R. in the " markedly improved " group, as a persistently high B.S.R. was found to exist throughout treatment in most of these cases. It has already been suggested that residual pain may be due to cartilage erosion and replacement fibrosis in a case in which the active disease has been arrested. This would be especially true of patients showing marked initial disability, and may well explain the fall in the B.S.R. occurring in a considerable proportion of patients showing no clinical improvement.

The association between change in B.S.R. and result might have been still closer had it been possible further to subdivide the " markedly improved " class. The difficulties involved in assessing the clinical results of treatment have already been emphasised, and a further subdivision of the " marked improvement " class has not been found practicable.

In most cases the clinical result tends to be proportional to the average fall in the B.S.R. It is significant that every case in the " cured " class had a normal B.S.R. after treatment, and the average fall in this group was greater than in any other class. The average fall in the " slight " and " no improvement " classes was very small.

The relationship between final B.S.R. and clinical result is shown in Table VI.

TABLE VI.—RELATIONSHIP BETWEEN FINAL B.S.R. AND CLINICAL RESULT

Clinical Result.	*Final B.S.R.*									*Average.*	*Total.*
	0–10	11–20	21–30	31–40	41–50	51–60	61–70	71–80	81–90		
Cured	29	1	—	—	—	—	—	—	—	4·9	30
Marked improvement	107	105	41	13	6	1	1	1	—	15·5	275
Moderate improvement	12	17	6	5	—	1	1	—	—	18·5	42
Slight improvement	5	5	2	4	—	1	—	—	—	21·0	17
I.S.Q. or worse ..	11	6	8	4	1	3	—	2	1	25·1	36
Total ..	164	134	57	26	7	6	2	3	1	16·1	400

Correlation coefficient +0·3169.

The association here has been shown to be somewhat closer than was the case in Table V. It would appear, then, from the above tables that clinical improvement is generally proportional to the fall in the B.S.R. and that the final B.S.R. gives some index of the clinical result. One must conclude, therefore, that the B.S.R. is of definite prognostic value as regards the extent of the fall and the final figure.

It has already been stated that no relationship exists between the initial and the final B.S.R. A significant association has, however, been shown to exist between the initial B.S.R. and the change in B.S.R. This is shown in Table VII., where it will be seen that that change is neatly proportional to the initial figure.

TABLE VII.—RELATIONSHIP BETWEEN INITIAL B.S.R., CHANGE IN B.S.R. AND THE FINAL B.S.R.

Class Interval.	*Initial B.S.R.* (*Mean*).	*Change in B.S.R.* (*Mean*).	*Final B.S.R.* (*Mean*).
0–10	5·0	+4·3	9·3
11–20	15·5	− 2·5	13·0
21–30	25·5	− 10·0	15·5
31–40	35·5	− 19·1	16·4
41–50	45·5	− 23·1	22·4
51–60	55·5	− 34·5	21·0
61–70	65·5	− 47·7	17·8
71–80	75·5	− 53·0	22·5
81–90	85·5	− 57·3	28·2
91–100	95·5	− 77·0	18·5

Correlation coefficient between initial B.S.R. and change in B.S.R. +0·7940.

B.S.R. and Relapse

Relapse has occurred eighty-one times in seventy-four cases. In thirty-three cases the immediately preceding B.S.R. was 10 mm. or less; it would appear from our findings, therefore, that a normal B.S.R. does not preclude the occurrence of relapse. On the other hand, there are many instances in the 400 cases where relapse has not occurred despite the fact that chrysotherapy has been discontinued when the B.S.R. was still high.

In fifty-one cases relapse was accompanied by an increase in the B.S.R. over the immediately preceding figure; the increase was 5 mm. or under in twenty cases, between 6 and 20 mm. in twelve, and over 20 mm. in eleven. In five cases the B.S.R. remained unchanged with the occurrence of relapse. In twenty-six instances a decrease in the B.S.R. as compared with the immediately preceding figure accompanied relapse. This decrease was 5 mm. or less in five cases and more than 20 mm. in three.

It is an interesting finding that the B.S.R. taken when relapse had actually occurred was 5 mm. or less in eight cases and between 6 and 10 mm. in seventeen cases. Attacks of acute fibrositis are, of course, common in rheumatoid arthritis, and it seems probable that the normal B.S.R. may be explained on the ground that the relapse in those twenty-five cases (and probably in many others) was not an actual flare-up of the arthritic lesion, but a fibrositis. Of the remaining cases, forty-eight had a B.S.R. of between 11 and 40 mm. and eight of 41 mm. and over.

B.S.R. and Toxic Reactions

Hartfall, Garland and Goldie (1937) have already pointed out that a proportion of the toxic reactions met with in chrysotherapy may be delayed for weeks or months after the end of the individual courses. As the 400 cases dealt with have been out-patients, and, further, as they have invariably been referred to their own doctors at the end of each course, no information is available regarding the B.S.R. in the majority of those cases having toxic reactions between courses. There is, however, sufficient information about toxic reactions during courses to make analysis worth while. In any case, it seems to be certain

that the B.S.R. would give little or no help in the prevention of toxic reactions which occur some time after the termination of a course, as the only means we have at the present time of averting reactions is the suspension of gold therapy.

In analysing the B.S.R.s associated with toxic reactions, only those taken two weeks or less before the onset of the toxic reaction have been considered. It is felt that if the B.S.R. is to be of any value in the avoidance of toxic reactions, as Savy (1935) has suggested, then any change must take place at least two weeks before their appearance, in order that the suspension of gold therapy may be effective.

The disturbances most frequently found involve the skin and consist of pruritus, erythemata, which may or may not be accompanied by desquamation and rarely exfoliative dermatitis. In all, there were six cases of pruritus alone where the B.S.R. was taken at the stated interval before its appearance. As these occurred in the early stages of the treatment, it might be expected that they would be associated with a high B.S.R. The actual figures found in the six cases were 4, 34, 7, 9, 9 and 40 mm., but in no case did this represent an increase over the previous B.S.R. In twenty-four cases of itching erythema the associated B.S.R. varied from 4 to 84 mm., the average being 18 mm. In three instances the figure associated with this type of reaction represented a slight increase over the previously found figure; but in view of the fact that in ten out of twenty-four cases the associated B.S.R. was less than 10 mm., it would appear that the B.S.R. will be of no value at all in foreseeing this type of reaction.

In the case of desquamating erythemata a similar state of affairs exists. In eleven such reactions the associated B.S.R. was under 10 mm. in eight cases, the figures for the other three cases being 32, 27 and 21 mm. Only in two of the latter three cases did the associated B.S.R. show any increase over that taken previously, and in both cases the difference was slight.

One case of exfoliative dermatitis had an associated B.S.R. of 29 mm.; this patient's B.S.R. was previously normal, but the increase from normal had taken place very gradually over about three months.

There was one case of herpes with an associated B.S.R. of 20 mm.; the preceding B.S.R. had been 38 mm.

In eight cases of sore mouth the associated B.S.R.s were 2, 2, 7, 22, 30, 22, 38 and 31 mm. In no case did the associated B.S.R. show any substantial increase over the preceding figure.

In three cases of diarrhœa the associated B.S.R. was 13, 12 and 5 mm.; in all three cases the B.S.R. was falling at the time of the toxic reactions. In ten cases of jaundice the associated B.S.R.s were 17, 18, 10, 12, 10, 15, 19, 18, 9 and 4 mm. The B.S.R.s in four cases of albuminuria were 6, 5, 41 and 38 mm. In one case of thrombocytopenic purpura the B.S.R., taken on the week of development of the purpura, was 5 mm.

From the above it will be seen that any type of toxic reaction can develop in association with either a normal or an abnormal B.S.R. It is apparent that the B.S.R. is of no help in the avoidance of even the most severe toxic reactions.

Discussion

It is admittedly a great drawback that a series of control figures for untreated cases is not available; so far as I am aware no such series has yet been published. The difficulty of obtaining a satisfactory control group is undoubted, and whether one would be justified in withholding all forms of treatment in a progressive and crippling disease such as rheumatoid arthritis over a long period of time is highly debatable. The introduction of chrysotherapy has altered the prognosis of this disease to so great an extent that every patient should be given the opportunity of benefiting from this therapy at the earliest stage. It has been shown previously (Hartfall, Garland and Goldie, 1937) that the results of chrysotherapy become significantly worse the longer the disease has lasted before the institution of this form of treatment, and the rapidity with which severe crippling can take place makes early treatment imperative.

That gold treatment produces a marked fall in the B.S.R. is certain, and the higher the initial figure the greater the fall; the ultimate effect seems to be to reduce the figures to a common level. While the initial figure is valueless from a prognostic point of view, the change in the B.S.R. is of definite value. The greater the fall and the lower the final figure, the better, on an average, is the clinical result. It is unfortunate that the "marked improvement" class included such a large proportion of the 400 cases. Had it been found practicable to subdivide

this class still further, it is probable that a closer association between final B.S.R. and result would have been found.

One of the most interesting features which has emerged from the analysis of these figures is that the mean fall in the B.S.R. is entirely determined by the fall taking place at the end of the first course. Ellman and Lawrence (1938) have suggested that dosage should be reduced whenever the B.S.R. falls to normal figures, in order that toxic reactions occurring later on in the treatment may be avoided. On the basis of the figures presented here it might be suggested that reduction of dosage should take place after the first course; whether subsequent courses consisting of, say, half the amount of gold salt used in the first course would be effective in stabilising the B.S.R. at its new level and in maintaining clinical improvement is a matter for trial. If some of the severe reactions encountered in second and subsequent courses, especially the hæmorrhagic ones, could be avoided by this means, one of the greatest disadvantages of gold treatment would be removed.

It has already been stated that no information is available regarding untreated cases over a long period of time. In this paper, however, it has been shown that, although a close association exists between initial B.S.R. and change in B.S.R., there is no definite relationship between initial and final figures. This raises the possibility that in a considerable number of untreated cases the B.S.R. would show wide fluctuations. This hypothesis receives support from the fact that a considerable proportion of the 400 cases shows a moderate increase in the B.S.R. after chrysotherapy and a small proportion shows a considerable increase. An alternative hypothesis is the assumption that chrysotherapy produces a non-specific upset which usually causes a fall in the B.S.R., but may cause a rise. The present-day view on the action of gold suggests that the latter theory is the correct one.

It is unfortunate, but not altogether unexpected, that according to the above figures the B.S.R. is of little value in anticipating either relapse or severe toxic reactions. The most severe upsets such as jaundice, severe albuminuria and aplastic anæmia have been seen in the presence of a normal B.S.R. The utility of the test is thus considerably lessened from a practical point of view.

Conclusions

1. A study of the blood sedimentation rate has been made in 400 gold-treated cases of rheumatoid arthritis observed over a period of time up to four years.

2. A considerable fall in the blood sedimentation rate has resulted in a large proportion of cases.

3. No relationship has been found to exist between the initial blood sedimentation rate and the clinical result.

4. The extent of the fall is entirely determined by the fall taking place at the end of the first course.

5. Clinical improvement is generally proportional to the fall in the blood sedimentation rate.

6. The blood sedimentation rate is of no value in anticipating toxic action or relapse.

I wish to express my gratitude to Dr. J. A. Fraser Roberts for invaluable help with some of the tables and calculations, and to Drs. S. J. Hartfall and H. G. Garland for allowing me to use their cases.

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THE ERYTHROCYTE SEDIMENTATION TEST: A WIDE-BORE TUBE METHOD USING OXALATED BLOOD AND PERMITTING CORRECTION OF THE RESULT TO A STANDARD RED-CELL VOLUME

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Introduction

The value of the sedimentation test in the study of patients suffering from rheumatic disease is today well recognised, but the lack of a uniform technique and of a uniform method of expressing the results of the test renders comparison of tests carried out in different clinics well-nigh impossible. The Empire Rheumatism Council, recognising this, have taken action by calling together a Sedimentation Test Sub-Committee of persons interested in the question of the standardisation of the test. The authors of this paper are among the members of that sub-committee and, stimulated by discussions therein, agreed to collaborate in establishing and perfecting a technique for the performance and for the recording of results of the sedimentation test which would enable the four hospitals to attain uniformity in this respect. This has been done, and today in the four largest British hospitals for rheumatic disease, which together admit more than 7,000 patients annually, results of the sedimentation test, which are entirely comparable one with another, are obtained by a uniform technique.

The purpose of this paper is to describe the origin of the method, to detail its technique and to assess its reliability, and also to discuss the various methods which have been tried for correcting the results for anæmia.

The authors wish to make it clear that the work now published does not at present bear the authority of the Empire Rheumatism Council, although it was inspired by the activities of that body. It is independent work which will in future be submitted to the E.R.C. Sub-Committee for their consideration,

and it is fully realised that the method involves certain procedures which other workers may not be prepared to adopt.

It is certain that there can be no single uniform method of doing the sedimentation test, because, for young children and others from whom venous blood cannot be obtained, a simple method, such as that of Payne (1932), capable of giving good results with a few drops of capillary blood, is of great value and cannot be discarded. When more blood can be procured for the test, and where there are adequate laboratory facilities, it seems desirable that a more elaborate method, such as the one now reported, which is sensitive, accurate and capable of correction for anæmia, should be used. The results obtained by this method appear to justify the additional complication of the test.

Derivation of the Method

A. The Tube.—The basis of the method is the use of a tube similar to that described by Zeckwer and Goodell (1925). The Zeckwer and Goodell tube is a 10 c.c. conical centrifuge tube which has the chief advantage of a very wide bore at its upper part where separation of cells commences. The tapered constriction of the lower end of the tube allows a longer column of blood to be used for a given volume. This tube has now been used with complete satisfaction by one of the authors for some twelve years (Race, 1929). It was concluded by another (Gibson, 1938), that of all the methods used, including most of the standard techniques, this was the most sensitive in detecting abnormal sedimentation and the most consistent in its results.

The first modification comprised the substitution of a 5 c.c. conical tube in place of the 10 c.c. tube in order that a smaller volume of blood should be needed for the test. This tube is of a similar shape to the larger tube and is graduated in 100 parts by volume (Fig. 1). It is supplied by the Scientific Glassblowing Co., Ltd. A comparison of the measurements of the two tubes shows that, in spite of the reduction of volume, there is no important difference in the length of the column of blood or of the bore of the upper part of the tube.

	Zeckwer and Goodell 10 *c.c. Tube.*	*New* 5 *c.c. Tube.*
Height of blood column	74 mm.	72 mm.
Diameter of upper end	15 mm.	12 mm.

The height of the blood column in the new tubes, as supplied by the manufacturer, is apt to vary from 70 mm. to 74 mm., as a

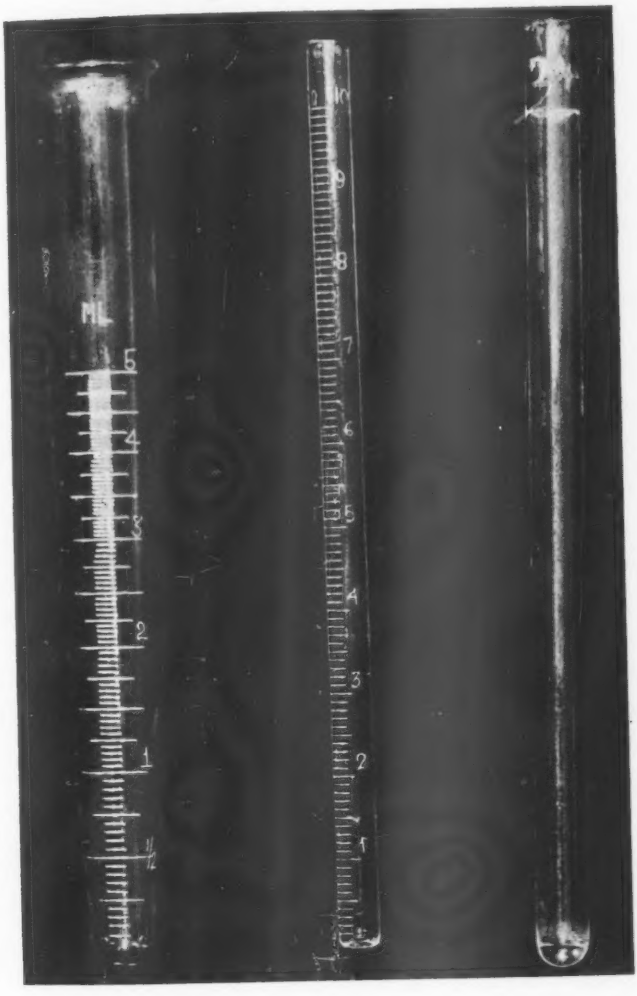

FIGURE 1.

The three tubes shown in the photograph are, from left to right:

(*a*) The 5 c.c. conical tube graduated in 100 parts by volume in which erythrocyte sedimentation is recorded.
(*b*) The Wintrobe hæmatocrit tube.
(*c*) A simple hæmatocrit tube made out of 5 mm. glass tubing with flattened bottom and 100 mm. mark etched on.

result of individual differences in the level at which tapering commences.

Before finally adopting the 5 c.c. tube in place of the 10 c.c.

tube, the reliability of which had long been proved, it was necessary to determine whether the results in the smaller tube were consistent with undiluted oxalated blood and whether the 5 c.c. tube gave results comparable with those given by the larger tube. To test these points the following experiments were carried out:

1. The new 5 c.c. tube was first tested to ascertain the consistency of its results. Duplicate tests were made simultaneously in two 5 c.c. tubes with sixty samples of blood. The following range of differences was observed in the two tubes:

No difference in 26 tests.				
1	per cent.	difference	in	22 tests.
2	,,	,,	,,	6 tests.
3	,,	,,	,,	5 tests.
4	,,	,,	,,	1 test.

Thus fifty-four out of sixty (90 per cent.) of the tests showed a difference of 2 per cent. or less, which figure represents approximately 1 mm. linear distance in the upper part of the tube. There was no difference greater than 4 per cent. The mean difference was 0·9 per cent. These figures define the experimental error likely to be associated with the use of the 5 c.c. tubes. The error is very small.

2. Duplicate tests were made on each of 224 blood samples in a 5 c.c. and a 10 c.c. tube. The following range of differences was observed:

No difference in 61 tests.				
1	per cent.	difference	in	75 tests.
2	,,	,,	,,	37 tests.
3	,,	,,	,,	31 tests.
4	,,	,,	,,	15 tests.
5	,,	,,	,,	3 tests.
6	,,	,,	,,	1 test.
7	,,	,,	,,	1 test.

Thus 173 out of 224 tests (77 per cent.) showed a difference of 2 per cent. or less, and only five tests (2·2 per cent.) showed a difference greater than 4 per cent. The mean difference was 1·5 per cent. Agreement between the results in the two tubes was therefore close, and there seemed no reason to suppose the 5 c.c. tube to be less accurate than the 10 c.c. tube for recording the erythrocyte sedimentation.

B. The Anticoagulant.—Fahraeus (1921) and others have shown that the rouleau-forming principle of plasma on which the sedimentation reaction depends is extremely susceptible to

dilution. Its concentration appears to be low, and its effects can be readily diminished or annulled by the addition of inert fluid. One effect of adding citrate solution to a sample of blood is, therefore, a retarding of the rate of sedimentation. At the same time, however, the increased dispersion of the cells, amounting to an artificial anæmia, tends to accelerate sedimentation. In some cases these antagonistic effects exactly balance one another, but in the majority of cases the retarding effect of plasma dilution predominates, as has been previously shown (Gibson, 1938). Experiments carried out on duplicate samples of oxalated and citrated blood in the new 5 c.c. tubes confirm this point.

Samples of blood were taken from fifty-two patients. From each patient an oxalated sample and a citrated (one part 3·8 per cent. sod. cit. to four parts blood) sample were obtained, and each was then put up in a 5 c.c. tube. The sedimentation was recorded at the end of one hour.

The following range of differences was observed in the two tubes:

No difference in	0	cases.			10 per cent. difference in	3	cases.		
1 per cent. difference in	1	case.			11	„	„	2	„
2	„	„	2	cases.	12	„	„	2	„
3	„	„	1	case.	13	„	„	3	„
4	„	„	3	cases.	14	„	„	3	„
5	„	„	6	„	15	„	„	2	„
6	„	„	3	„	16	„	„	0	„
7	„	„	8	„	17	„	„	0	„
8	„	„	7	„	18	„	„	1	case.
9	„	„	5	„					

Only three out of fifty-two (5·8 per cent.) of these tests showed a difference of 2 per cent. or less. A difference greater than 4 per cent. was noted in forty-five (86·3 per cent.) of the tests and the mean difference was 8·3 per cent. In the great majority of instances the rate of sedimentation was slower in the citrated sample than in the oxalated. In only seven tests (13·5 per cent.) was the rate more rapid in the citrated blood.

Gibson (1938), using the Westergren tube, previously found that 15·2 per cent. of duplicate tests proved to be more rapid in the citrated blood, and the majority showed a slowing of the rate with citrate. The mere fact that the same treatment results in acceleration of the rate in some 15 per cent. of blood samples, instead of the usual slowing, indicates the complexity of the test and the complications introduced by citrate dilution.

If the degree of plasma dilution and red-cell dispersion were

constant, the error would always be the same, but both depend upon the relative proportions of plasma and red cells present in any particular sample of blood. For example, if one part of citrate were added to four parts of whole blood from each of two patients, one of whom had a red-cell volume of 25 per cent. and the other a red-cell volume of 50 per cent., the dilution of the plasma in the first case is one part citrate to three parts plasma, and in the second, one part citrate to two parts plasma. In each case the dispersion of the red cells is also significantly different. Dilution of the plasma, therefore, introduces an important and imponderable variable.

Wintrobe and Landsberg (1935) have shown that in tubes of wide bore, oxalate in the proportion of 2 mgm. per 1 c.c. of blood does not materially influence the sedimentation reaction when compared with that obtained in heparinised blood. This concentration of oxalate has been adopted, and pure potassium oxalate has been used in preference to a mixture of potassium and ammonium oxalates, as the latter renders the blood sample useless for urea or plasma protein estimations, both of which are sometimes called for in rheumatic patients.

A further consideration which influenced agreement on the use of oxalate anticoagulant was the practical one of error in dilution when mixing blood and citrate solution in the collecting syringe. Moreover, the mixture so obtained is useless for hæmatological or chemical examinations.

The authors are of opinion that neither convenience nor accuracy is gained from the use of citrate anticoagulant. But at the same time it must be recognised that when the volume of blood obtainable is small, as in children, a narrow-bore tube is required to secure an adequate height of blood column, and under these circumstances dilution of the blood is necessary since undiluted oxalated blood does not fall regularly in such narrow tubes. They therefore agree with Schuster (1939) that in narrow tubes citrated diluted blood gives more regular results than undiluted oxalated blood.

C. Correction for Anæmia or Polycythæmia.—It was felt that a necessary perfection to any sedimentation test should be the ability to correct the results for deficiency or excess of red cells. This seemed especially desirable as the test would be used as a main laboratory index for the diagnosis and control of cases of chronic arthritis in whom there are often found marked

variations of red-cell size and hæmoglobin content and of plasma volume. As a result of preliminary trials of many methods of standardisation it was decided to adopt the principle of Walton (1933), whereby the blood is adjusted experimentally to a standard red-cell content before the test. It has been shown (Collins, 1935) that the anæmia in the chronic rheumatic diseases is most frequently of a hypochromic type with diminished hæmoglobin content but a relatively normal red-cell count, and as the influence of anæmia on sedimentation seems to depend on the relative volume concentrations of red cells and plasma it was decided to standardise the test according to the packed cell (hæmatocrit) volume rather than according to the red-cell count, as described in the original Walton technique. The packed red-cell volume (P.C.V.) is more rapidly obtained than the count, provided that a centrifuge is available for its estimation, and the hæmatocrit tube has a smaller experimental error than the red-cell counting chamber.

These, then, were the principles upon which the method under discussion was based: (*a*) the use of a 5 c.c. graduated conical sedimentation tube of wide bore in its upper part to allow of free fall, (*b*) the use of dry oxalate as anticoagulant, and (*c*) the correction of the test to a standard P.C.V. by suitable adjustment of the plasma-cell volume ratio.

Each of the authors commenced the operation of the test in his laboratory on an agreed technique whereby sedimentation was recorded in undiluted blood (crude S.S.), and also in the blood brought to a standard red-cell volume by suitable addition or subtraction of plasma (experimentally corrected S.S.). For reasons to be discussed later, it was thought better to record the results as suspension stability (S.S.) rather than sedimentation rate, the S.S. being the percentage volume of red-cell suspension measured at the end of one hour.

Method of Estimating Crude S.S. and Experimentally Corrected S.S.

Well mixed oxalated blood from the patient was distributed in the following way:

1. Seven c.c. were pipetted into a plain test-tube (Tube 1).
2. Five c.c. were placed direct into a 5 c.c. sedimentation tube (Tube 2) for estimation of crude S.S.

3. A 100 mm. hæmatocrit tube of Wintrobe type was filled to the mark and centrifuged at 3,000 r.p.m. for fifteen minutes. The P.C.V. was then read off (x per cent.).

4. The patient's own plasma was then added to or removed from the 7 c.c. of blood in Tube 1 in such a way that this volume then became $\frac{x}{6}$ c.c. This manipulation brought the packed cell-volume to the chosen standard of 42 per cent.

5. Five c.c. of the adjusted blood were then transferred after thorough shaking to a second 5 c.c. sedimentation tube (Tube 3).

6. Tube 2 was then re-shaken and the sedimentation of the blood in Tubes 2 and 3 were recorded at half-hourly intervals for two hours. It was soon apparent that the one-hour reading gave the most satisfactory index of the erythrocyte sedimentation and all results have been expressed in terms of this one-hour reading.

The standardising P.C.V. of 42 per cent. was chosen for three reasons: (*a*) It was known from previous experience (Gibson, 1938) that oxalated, undiluted blood of this P.C.V. fell with regularity in a tube of wide bore. (*b*) The mean P.C.V. of 400 consecutive rheumatic patients of both sexes was 42·08 per cent. (*c*) It is the mean normal value for women.

By this method three figures were recorded for each test—the "crude S.S." of the unmodified blood, the "experimentally corrected S.S." of the blood adjusted to the standard 42 per cent. P.C.V., and the P.C.V. (hæmatocrit) of the blood sample.

Calculations for Correction of the S.S.

Theoretically the method detailed above appeared to be excellent, but in hospital practice the adjustment of a large number of blood samples before the tests could be set up proved to be very laborious. Attempts were then made to find a method of calculating the "corrected S.S." from the "crude S.S." and the P.C.V. Each of the authors worked on this problem independently, and each proposed a different correction calculation. These four methods for calculating the "corrected S.S." are described below:

Method I.—The author of this method recorded a number of tests made on different blood samples resulting in identical experimentally corrected S.S. On plotting the "crude S.S."

against the P.C.V. of the blood samples, it was noticed that the curve so formed approximated closely to the basic curve used by Wintrobe and Landsberg (1935) for the compilation of their graphs for correction of the S.R. in their narrow 100 mm. tubes. The Wintrobe and Landsberg chart was accordingly used for the computation of the corrected values. Later experience showed, however, that bloods with P.C.V. widely diverging from the normal failed to behave on experimental correction according to this calculation. This difference from Wintrobe and Landsberg's findings was doubtless due to the considerable difference in bore of the tubes used in the two methods.

METHOD II.—The author of this method felt that even if no curve or factor could be found, it would be of service if a large number of observations were tabulated in such a way that for a wide range of "crude S.S." and hæmatocrit readings a corrected figure could be obtained by reference to a previous sample in which experimental correction had been undertaken.

From observations on 351 blood samples such a table was constructed in which for each hæmatocrit and crude S.S. value the difference between the crude and the experimentally corrected S.S. was recorded. These data are summarised in Table I.

From a study of these figures it was at once seen that the results were somewhat variable, and that modification of the cell-plasma ratio in certain cases introduces complicating factors for which there is at present no explanation. Such anomalous cases were exceptional. The general tendency was for the difference between the crude and the experimentally corrected S.S. figures to increase steadily as the hæmatocrit P.C.V. of the blood sample rose above or fell below 42 per cent. On the other hand, among bloods of the same P.C.V. there was little tendency for the difference to be proportional to the crude S.S. It seemed likely, therefore, that a rough correcting calculation might be possible by taking the crude S.S. and adding or subtracting the mean difference corresponding to the P.C.V. of the blood sample.

A fuller examination of the data showed an interesting relation between the mean-difference figures and the P.C.V. For P.C.V. below 42 per cent. the S.S. showed a difference of approximately 1·5 for each 1 per cent. decrease in P.C.V. Thus the figure to be added to the crude S.S. could be found with fair accuracy by subtracting the patient's hæmatocrit P.C.V. from 42 per cent. and multiplying this difference by 1·5. When the

blood sample was more than 42 per cent. P.C.V. the mean difference was approximately 1·0 for each 1 per cent. excess P.C.V. Thus the figure to be subtracted from the crude S.S. in bloods of P.C.V. greater than 42 per cent. could be calculated simply by subtracting forty-two from the patient's hæmatocrit reading.

TABLE I.—DATA FROM 351 COMPLETE TESTS UPON WHICH CALCULATION METHOD II. WAS BASED.

P.C.V. of Blood Samples. (Per Cent.)	*Number of Tests.*	*Aggregate Differences between Crude and Exp. S.S.*	*Mean Difference.*	*Mean Difference ÷ (42 – P.C.V.)*
29	4	74	18·5	1·4
30	7	129	18·4	1·5
31	3	38	12·7	1·2
32	5	76	15·2	1·5
33	7	91	13·0	1·4
34	7	81	11·6	1·5
35	10	110	11·0	1·6
36	7	75	10·7	1·8
37	21	151	7·2	1·4
38	22	130	5·9	1·5
39	33	159	4·8	1·6
40	37	116	3·1	1·6
41	30	61	2·0	2·0
				Mean Difference ÷ (P.C.V. – 42).
43	24	25	1·0	1·0
44	27	64	2·4	1·2
45	32	111	3·5	1·2
46	16	65	4·1	1·0
47	23	107	4·6	0·9
48	11	67	6·1	1·0
49	11	82	7·5	1·1
50	7	58	8·3	1·0
51	5	42	8·4	0·9
52	2	27	13·5	1·4

Table II. shows a recalculation of these factors from a total of 500 tests (351 tests by the author of this method, shown in Table I., and a further 149 tests made independently by the other authors). It will be seen that for hæmatocrit readings below 42 per cent. the factors vary little about the approximate mean of 1·5, and for hæmatocrit readings above 42 per cent. the factors are all approximately 1·0.

TABLE II.—DATA FROM 500 COMPLETE TESTS CONFIRMING THE VALIDITY OF THE FACTORS ARRIVED AT IN METHOD II.

P.C.V. of Blood Samples. (Per Cent.)	*Number of Tests.*	*Aggregate Differences between Crude and Exp. S.S.*	*Mean Difference.*	*Mean Difference ÷ (42 – P.C.V.)*
26	2	47	23·5	1·5
27	1	26	26·0	1·7
28	2	49	24·5	1·8
29	5	94	18·8	1·4
30	9	162	18·0	1·5
31	5	75	15·0	1·4
32	12	177	14·8	1·5
33	10	141	14·1	1·6
34	14	172	12·3	1·5
35	19	209	11·0	1·6
36	17	170	10·0	1·7
37	33	243	7·4	1·5
38	36	229	6·4	1·6
39	50	237	4·7	1·6
40	48	154	3·2	1·6
41	31	62	2·0	2·0
				Mean Difference ÷ (P.C.V. – 42).
43	30	33	1·1	1·1
44	35	85	2·4	1·2
45	40	140	3·5	1·2
46	22	93	4·2	1·1
47	30	148	4·9	1·0
48	16	95	5·9	1·0
49	14	102	7·3	1·0
50	9	80	8·9	1·1
51	6	57	9·5	1·1
52	4	45	11·3	1·1

On theoretical grounds, assuming that the rate of rouleau formation depends upon a simple property of plasma only, the graph of correction ought to be a curve of the type used by Rourke and Ernstene (1930), Wintrobe and Landsberg (1935), Hambleton and Christianson (1937-38) and others; but as the sedimentation of blood is no simple event which obeys simple mathematical laws, there is no reason to suppose that a smooth curve is a more accurate correction graph than the refracted straight line based on the two factors. Furthermore, any attempt to round off a curve might suggest an accuracy greater than our data warrant. The method is a practical one involving a very simple calculation. It may be summarised thus:

1. Determination of the "crude S.S." of undiluted oxalated blood.

2. Estimation of P.C.V. of the blood sample by centrifuging in a hæmatocrit tube for fifteen minutes at 3,000 r.p.m. (It is as well to test the performance of any centrifuge by spinning a test batch of filled hæmatocrit tubes until a constant P.C.V. is reached and noting the time required by the machine to achieve this.)

3. Correction of "crude S.S." by:

(*a*) If P.C.V. of blood is less than 42 per cent., adding 1·5 (42 – P.C.V.).

(*b*) If P.C.V. of blood is more than 42 per cent., subtracting 1 (P.C.V. – 42).

METHOD III.—The correction curves in this method were obtained as follows: A comparatively large sample of blood was collected and divided into at least three parts, which parts were then, by addition or subtraction of plasma, manipulated to three or more different P.C.V.s, and the S.S. was determined at each P.C.V. The results were plotted and the points joined by a smooth curve. From a large series of such experiments a chart of multiple curves was constructed and the crude stabilities were corrected by noting the point of intersection of vertical and horizontal lines drawn from the P.C.V. and crude S.S. values respectively, and following the nearest curve to its intersection with the vertical line at the standard C.V. of 42 per cent.

METHOD IV.—This method depended on the use of correction factors by which the P.C.V. difference from 42 per cent. was to be multiplied, but it differed from Method II. in that multiple factors were established and that these factors were grouped according to the range of corrected S.S. Like Method II., different factors were found to be necessary for bloods above 42 per cent. and for those below 42 per cent. The factors were the average slopes of correction lines for bloods whose corrected S.S. fell within groups of ten integers. The correction lines were obtained from 158 blood samples in the following way:

For every sample, the crude S.S. and the experimentally corrected S.S. were plotted on a graph whose abscissa represented P.C.V. per cent. and whose ordinate represented S.S. values. Each pair of points was joined by a straight line. The experimentally corrected S.S. points, of course, always lay on the vertical line representing 42 per cent. P.C.V. The slope of each line was

expressed as the tan of the angle—*i.e.*, the difference between crude S.S. and corrected S.S. divided by the difference between P.C.V. of the blood and 42 per cent.

It was found that these slopes could be grouped with fair accuracy according to the range of corrected S.S. in the following way:

(*a*) Where observed P.C.V. was below 42 per cent.:

No. of Cases.	*Corrected S.S. Range.*	*Slope of Average Correction Line.*
13	100 to 90	1·61
24	89 to 80	1·82
24	79 to 70	2·00
22	69 to 60	1·68
16	59 to 50	1·45

(*b*) Where observed P.C.V. was above 42 per cent.:

11	100 to 90	0·83
22	89 to 80	1·17
11	79 to 70	1·53
7	69 to 60	1·64
8	59 to 50	1·88

The average slope figures in the last column are the factors by which the P.C.V. difference from 42 per cent. was multiplied to obtain the difference between crude and corrected S.S.

In order to determine which correction factor to apply for any test, it was necessary to find the point representing crude S.S. and original P.C.V. on a large scale graph on which the average correction lines were drawn. The graph was divided by these lines into areas to which the different correction factors applied, and it was then simply necessary to use the factor for the appropriate area.

This method has been described in some detail because it was the only correction method which employed multiple factors, and it is extremely interesting to compare the accuracy of these multiple factors with the simple factors employed in Method II.

Comparison of "Corrected S.S." obtained by the Four Calculation Methods with "Corrected S.S." obtained by Experiment

In order to test the accuracy of our four correction calculations when applied to tests wherein the experimentally corrected S.S. had been determined, a system of "blind" corrections was

evolved. Each of the authors performed fifty complete tests, recording the crude and experimentally corrected S.S. and the P.C.V. The crude S.S. and the P.C.V. figures were then circulated to each of the other authors, who calculated the corrected S.S. according to his own method and returned the figures to be checked against the corrected S.S. which had been determined by experiment. In this way each author performed fifty complete tests and calculated corrections for a total of 200 tests. Except for the fifty tests which he himself had carried out, he was ignorant of the experimentally corrected results at the time of his calculations.

The four sets of calculated corrections have since been correlated with the experimental corrections and the deviations of the former from the latter in the 200 tests are recorded in Tables III. and IV.

It is obvious from the statistical analysis of the results of our different methods of calculating the corrections for different hæmatocrit readings that all the methods gave reasonably accurate determinations. Method I. is statistically inferior to the other three methods, but any of the latter would meet all practical requirements.

It remained to decide which method should be adopted and recommended for general use. The choice fell unanimously on Method II. because of the extreme simplicity of the calculation. From Table IV. it will be seen that the difference between the experimentally observed corrected S.S. and that calculated by this method was 4 per cent. or less in over 90 per cent. of cases. It may be noted that 4 per cent. represents a linear fall of about 2 mm.

This method has been described in detail above (p. 341). It may be useful to construct a simple table of the necessary amounts to be added to or subtracted from the "crude S.S." at each hæmatocrit volume to obtain a result corrected to the standard P.C.V. of 42 per cent.

It is of no material value to report the corrected S.S. as a figure containing a 0·5 value, and to maintain all our results as integers we have adopted the practice of raising any corrected S.S. containing this fraction to the nearest whole number above. Thus a crude S.S. of 64 in a blood of 35 per cent. P.C.V. when corrected by Method II. yields the figure of 74·5. This is reported as 75.

TABLE III.—FREQUENCY DISTRIBUTION OF DEVIATION OF CALCULATED CORRECTED S.S. FROM OBSERVED S.S. IN BLOOD EXPERIMENTALLY CORRECTED TO 42 PER CENT. P.C.V.

Relation of Calculated to Observed Correction.	*Corrections Calculated by :*			
	Method I.	*Method II.*	*Method III.*	*Method IV.*
−22	—	—	1	—
−21	—	—	—	—
−20	—	—	—	—
−19	—	—	—	—
−18	—	1	—	—
−17	—	—	—	—
−16	—	—	—	—
−15	—	—	—	—
−14	—	—	—	—
−13	—	1	—	—
−12	—	—	1	—
−11	—	—	—	1
−10	—	—	—	—
− 9	—	—	—	—
− 8	—	1	—	—
− 7	3	—	—	4
− 6	4	2	3	1
− 5	2	5	3	4
− 4	7	4	3	8
− 3	15	10	10	6
− 2	15	20	18	15
− 1	25	27	28	29
0	43	57	51	40
+ 1	22	34	38	37
+ 2	23	15	13	20
+ 3	12	12	10	12
+ 4	6	4	13	10
+ 5	8	3	3	8
+ 6	4	3	3	1
+ 7	1	—	—	1
+ 8	4	—	1	1
+ 9	1	1	1	1
+10	1	—	—	1
+11	2	—	—	—
+12	2	—	—	—
+13	—	—	—	—
Total cases ..	200	200	200	200
Standard deviation	3·4	2·8	3·0	2·9

TABLE IV.—DEVIATIONS OF (*a*) 2 PER CENT. OR LESS; (*b*) 4 PER CENT. OR LESS OF CALCULATED CORRECTED S.S. FROM EXPERIMENTALLY CORRECTED S.S.

(Each group contained 50 cases.)

Tests carried out by :	*Corrected S.S. Calculated by :*			
	Method I.	*Method II.*	*Method III.*	*Method IV.*
(*a*) *Differences of 2 per cent. or less :*				
The author of I.	28	28	31	27
The author of II.	25	42	30	27
The author of III.	36	40	49	41
The author of IV.	39	43	38	46
Totals (200 tests)	128	153	148	141
(*b*) *Differences of 4 per cent. or less :*				
The author of I.	42	43	41	41
The author of II.	35	48	47	38
The author of III.	42	44	47	49
The author of IV.	49	48	49	49
Totals (200 tests)	168	183	184	177

ANOMALOUS RESULTS

1. INCONSISTENT SEDIMENTATION.—Two groups of anomalies have been encountered in the course of this study. The first, which is described by the term "inconsistent sedimentation," is a failure of the red cells to separate from the plasma after being set up in the sedimentation tube; but separation takes place after re-shaking the blood, or it may occur normally in a duplicate test with the same blood sample. This anomaly has been described by Shackle (1938). It is not to be explained by clotting, inadequate tube-bore, high red-cell volume, low temperature, or any of the usual causes of retarded fall. Nor does it occur twice in blood samples from the same patient. It is an inconsistent defect unlike the anomalous sedimentation in anæmia described below.

Instances of this phenomenon are rare. They do not appear more than once or twice in some thousand tests. They may usually be recognised by observing the sedimentation in two tubes of two portions of the same blood sample. For this reason one of the authors invariably records the sedimentation in the hæmatocrit tube before centrifuging as a check on the sedi-

mentation in the 5 c.c. tube, but in one observed case retardation occurred in both tubes. A repeat test, however, will not give the same false result.

Instances of the phenomenon are given below:

Date.	1 *Hour S.S.*		*P.C.V. per Cent.*	*Corrected S.S.*
	5 c.c. Tube.	*Hæmatocrit Tube.*		
Case 2,026: Rheumatoid arthritis; female, aged sixty.				
23/12/38	37	34	26	61
27/2/39	*92*	*92*	29	*112*
27/2/39 (re-shaken)	42	—	29	62
27/5/39	43	43	30	61
Case 1,438: Rheumatoid arthritis; male, aged sixty.				
12/4/38	49	47	36	58
31/5/38	50	48	36	59
8/9/38	52	47	37	60
28/2/39	*92*	36	34	*104*
28/2/39 (re-shaken)	46	—	34	58
Case V.Y.: Rheumatoid arthritis; female, aged seventy-one.				
9/5/39	*94*	—	30	*112*
9/5/39 (re-shaken)	45	—	30	63
Case 3,417: Old rheumatoid arthritis; female, aged seventy-two.				
22/4/39	*98*	52	35	*109*
22/4/39 (re-shaken)	47	—	35	58

In case 2,026 an anomalous result was obtained for the second test in both the 5 c.c. tube and the hæmatocrit tube. The fact that this was an inconsistent sedimentation and not a deficiency of the sedimentation factors in the plasma associated with anæmia (see below) was recognised by comparison with the test performed two months earlier. Re-shaking of the sample resulted in proper sedimentation.

In the other cases the rapid sedimentation in the hæmatocrit tube or of the blood remaining in the collecting tube indicated the anomalous result in the other tube. The calculation of corrected S.S. to over 100 also showed something to be amiss with the test.

2. Anæmia in the Absence of Diminished Suspension Stability.—Anæmia may undoubtedly occur without an increase in the rate of sedimentation. In certain cases of anæmia not only the cells may be deficient, but the plasma may also

lack the constituents which make up the rouleau-forming principle. Recovery from the anæmia may mean not only a return of the red cells to normal number and hæmoglobin content, but also a recovery of the plasma deficiency. As an example the following case of pernicious anæmia may be quoted: At the time of the first sedimentation test the patient had 1,420,000 R.B.C.s and a colour index of 1·4. The P.C.V. at this time was only 17 per cent., a very abnormal blood in which to record sedimentation. As a check on this test, therefore, the same blood was manipulated by the addition of red cells to a P.C.V. of 32 per cent. and re-tested.

Date.	*Crude S.S.*	*P.C.V. per Cent.*	*Corrected S.S.*
9/12/38	54	17	92
9/12/38 (adjusted) ..	80	32	95
17/1/39	84	38	90
13/4/39	87	42	87

It is to be noted that recovery from anæmia was accompanied by a diminishing, not increasing, corrected S.S. Hence, the phenomenon described by Gregg (1936-37) in rabbits, and by Schuster (1938) in man, may occur—viz., anæmia masking an increased rate of sedimentation with the latter becoming apparent as the red-cell count and volume improve. Such a sequence would of course upset any method of correction. This state of affairs is somewhat rare in rheumatic patients, and can be recognised in bloods by the corrected suspension stability approaching or even exceeding 100. The sedimentation test is fundamentally an attempt to assess the presence or absence of certain conditions of the plasma, and this is one of the conditions which may be identified by the test. Without correction for P.C.V. such an abnormality would be missed and the blood might be reported as normal. When this condition is recognised it should be reported to the physician that the patient's blood is abnormally deficient in sedimenting factors and that the sedimentation test should be disregarded in arriving at a diagnosis.

In a total of 2,012 patients observed at Centre II. only eight such cases have been noted. Generally these cases had a crude S.S. of eighty or more, with a P.C.V. of 35 per cent. or less, and they were women. In this series the condition occurred in about

0·8 per cent. of all female rheumatic patients, but a more accurate impression of its incidence is conveyed by the fact that it occurred in 2·6 per cent. of all women in this hospital with a normal (more than eighty) S.S. Its frequency in uncomplicated hypochromic anæmia is not known. Cutler *et al.* (1938) have also remarked on this condition. The eight cases from Centre II., together with five cases from other centres, are tabulated below as examples of their identification (Table V.).

TABLE V.—CASES WITH ANÆMIA AND NORMAL SEDIMENTATION TEST.

Clinical Features.	*Sex.*	*Age.*	*Crude S.S.*	*P.C.V. per Cent.*	*Corrected S.S.*
Severe rheumatoid arthritis ..	F.	25	78	28	99
Subacute rheumatic infection ..	F.	28	84	31	101
Old Still's disease	F.	29	82	32	97
Rheumatoid arthritis	F.	45	84	32	99
Rheumatoid arthritis	F.	26	80	33	94
Early osteo-arthritis	F.	49	88	33	102
Subacute rheumatic infection ..	F.	16	90	35	101
Fibrositis	F.	28	91	35	102
Fibrositis	F.	42	95	36	104
Fibrositis	F.	34	84	23	113
Rheumatoid arthritis	F.	65	88	31	105
Old Still's disease	M.	16	93	35	104
Non-rheumatic	M.	27	95	34	107

The following repeated tests on the third of these patients may be quoted to show that this anomalous result is consistently repeated in different blood samples from the same patient. The point has been mentioned before in discussing the nature of the inconsistent sedimentation in the previous section:

Date.	*Crude S.S.*	*P.C.V. per Cent.*	*Corrected S.S.*
31/3/37	79	32	94
11/5/37	82	32	97
12/5/37	87	32	102
7/6/37	84	33	98
9/11/37	86	34	98

The Value of Corrected S.S. in Rheumatism

Repeated sedimentation tests are frequently performed to control or to assess the value of treatment in rheumatism. In chronic rheumatism particularly it is the practice to administer hæmatinics in addition to therapy directed at the rheumatic process, and improvement in the anæmia may well account in a large measure for the improvement in the sedimentation rate observed in a crude (uncorrected) test. Alternatively the use of drugs (*e.g.*, gold preparations) which are toxic to the hæmatopoietic system may induce an anæmia and accelerate the rate of sedimentation in the crude test. Such errors in the follow-up of cases can be largely discounted if a corrected sedimentation test result is also available. Two cases, from Centre I., illustrating these points are abstracted below:

Case 1.—Mrs. M. B., aged twenty-seven. Typical rheumatoid arthritis for three years. Sedimentation tests performed on admission (17/2/39) and five and a half weeks later (26/3/39). Meanwhile the patient had received hæmatinics as well as other treatment. The apparent improvement in the S.S. is seen from the corrected figures to be mainly due to recovery of the anæmia:

Date.	*Crude S.S.*	*P.C.V. per Cent.*	*Corrected S.S.*
17/2/39	55	32	70
28/3/39	66	40	69

Case 2.—Mr. A. S., aged thirty-nine. Rheumatoid arthritis for nine months, rapidly advancing. Irregular pyrexia. Sedimentation tests were made shortly after admission (20/3/39) and again three and a half weeks later. Small doses of gold salts had been administered meanwhile, but the patient had responded badly and had become anæmic. The apparent fall in the S.S. is seen from the corrected figures to be attributable to the increasing anæmia:

Date.	*Crude S.S.*	*P.C.V. per Cent.*	*Corrected S.S.*
20/3/39	57	43	56
12/4/39	46	35	57

In addition to the value of the corrected S.S. in the follow-up of cases, it is of obvious value in estimating the true activity of a disease by its effect on the sedimentation factors in the plasma dissociated from its effects on the red-cell number and volume.

Value of the Hæmatocrit as an Independent Index of Abnormality in Rheumatism

The hæmatocrit tube described by Wintrobe (1933) and obtainable from most instrument makers may be used. This tube holds a 100 mm. column of blood and is about 2·5 mm. in diameter. Cheaper and equally satisfactory, however, is a 5 mm. bore tube which can be made in any laboratory from 5 mm. glass quill tubing. One end is sealed off and the bottom flattened by means of a heated metal rod of the appropriate diameter, and the 100 mm. filling-mark is etched on (Fig. 1). This tube has the additional advantage that it may be filled and set up for a duplicate observation of the S.S. before centrifuging. Its bore of 5 mm. allows a freer fall of oxalated blood than does the narrower tube, and the duplicate reading, though not reported, may prove a useful check on the 5 c.c. tube in cases of inconsistent sedimentation. Reading of the S.S. and of the P.C.V. after centrifuging is effected by holding the tube vertically against a millimetre scale. This tube holds 2·0 c.c. of blood.

It has been the experience of the authors that the additional labour involved is more than repaid by the additional information afforded by the hæmatocrit reading. The various uses of the hæmatocrit tube have been fully described by Wintrobe (1933). Apart from its importance in the interpretation of the sedimentation test it is itself an independent means of estimating anæmia or abnormal plasma volume. Both of these are of particular importance in rheumatism. Collins (1935) has described the anæmia commonly co-existing with chronic rheumatism, and Gibson and Kersley (1938) have described it in terms of cell-plasma volume ratio. In fibrositic conditions the packed cell volume is substantially normal, whereas in rheumatoid arthritis and ankylosing spondylitis a normal value is uncommon. After a short experience with the hæmatocrit it becomes a habit to think of anæmia in terms of red-cell volume, and in a busy laboratory this method of assessing and controlling the progress of anæmia saves many hours of painstaking cell counting. The readiness with which toxic failure of the blood-forming organs in the course of gold therapy can be identified is exemplified in Case 2 quoted above.

The depth of the leucocyte cream observed in the hæmatocrit tube is also an indication of any gross departure from normal of

the white cell count. In one case the first indication of a lymphatic leukæmia in a case of " osteoarthritis " was the observation of a leucocyte volume of 6 per cent. When the white cell count was subsequently made in this case it was 120,000 per c.mm. Finally, the plasma colour may be of assistance in recognising icterus in its sub-clinical stages, and the use of a hæmatocrit tube 100 by 5 mm. gives a volume of plasma sufficient for the performance of the Van den Bergh test. The application of this in rheumatism and gout is in association with possible liver damage from gold or atophan treatment.

In short, the hæmatocrit tube provides, with the minimum of labour, a brief hæmatological review and indicates at a glance those cases in which more detailed investigations would be profitable.

The hæmatocrit volume is not to be identified with the hæmoglobin content of the blood except in a very general way. Variations in red cell size, number, and hæmoglobin content of individual cells may combine to produce packed cell volume and total hæmoglobin figures which are not necessarily correlated. Twelve bloods which had a P.C.V. of exactly 42 per cent. had hæmoglobin contents, estimated by the Hellige Neoplan method, ranging from 87 to 98 per cent., with a mean of 92·6 per cent. (12·4 to 13·8 gm. per cent., mean 13·09 gm. per cent.). The hæmatocrit tube has also been used by Wintrobe (1933) and Wintrobe and Landsberg (1935) as a sedimentation test-tube, but its bore is considered to be too narrow for accurate results with bloods of high red-cell volume. The hæmatocrit tube, therefore, is used only as an auxiliary part of the test which is made in the large 5 c.c. tube.

Suspension Stability or Sedimentation Rate ?

In the method of the sedimentation test which has been described the actual measurement which is read off the sedimentation tube at the end of one hour is a measurement of volume—the volume occupied by the suspension of red cells, or, alternatively, the volume of supernatant plasma which has been cleared of red cells. If the latter figure is read and recorded as the sedimentation rate (S.R.), it must be clearly understood that it deals with a volume rate per hour and not with a linear distance fall per hour, which is usually implied in other methods in which the S.R. is the recorded result. In parallel-sided tubes

this linear fall per hour is also a volume fall per hour, but a complication is introduced in the tube that is used in this work by its tapering lower part, which interferes with packing of the cells so that in rapidly sedimenting bloods, which approach packing at the end of one hour, comparison of volume rate in the conical tube and linear rate in the straight tube may be fallacious. For these reasons all the results have been recorded as suspension stability—*i.e.*, the volume of red-cell suspension still standing at the end of one hour. The figure 100 – S.S. may, however, generally be considered the sedimentation rate, provided that the reservations mentioned above be held in mind.

Comparison with Other Techniques

It is not proposed to discuss this matter fully here. The particular advantages of certain of the measures employed in the new test have already been indicated. Suffice it to say that each of the authors has been so favourably impressed with the reliability and uniformity of the results of the new method that it has been established as the routine method in the laboratories and institutions represented, and that it has been thought fit to replace other methods which were in use at the time of its introduction (viz., the 10 c.c. tube method, the Westergren tube and the Walton techniques). The decisions, which were individually arrived at, were reached after consideration had been given to parallel tests by two methods and to clinical applications.

Limits of Normality and Manner of Recording Results

It has not been found possible to make sedimentation tests on a large series of healthy persons such as were available to Wintrobe and Landsberg (1935). Each of the authors, however, tested a number of presumably healthy persons, colleagues, assistants, and blood donors, but they do not feel in a position to state a definite numerical limit of normality for the test. No such hard-and-fast limit exists, for reduced stabilities are to be found on occasion in apparently healthy persons and high stabilities are sometimes encountered in obvious disease. The test is a test for presence or absence of an excess of rouleau-forming principles in plasma. It is not a direct test for the presence or absence of disease, but in certain diseases, including rheumatism

and tuberculosis, the results of the test are well known to bear a close correlation to the clinical activity and prognosis of the disease. Experience with this new method of conducting the sedimentation test only permits the statement that a corrected S.S. below eighty to eighty-five is of clinical significance. Results higher than eighty to eighty-five are likely to be normal.

Throughout this paper the aim has been to give greater precision to the numerical expression of the results of the sedimentation test. It is recognised that a numerical record of the S.S. is merely an index of a complicated phenomenon and not an absolute number, as is the figure expressing, for example, P.C.V. percentage or concentration of uric acid in blood.

The only alternatives in reporting the sedimentation test are: firstly, in general terms, such as normal, slightly or markedly increased or diminished; secondly, by a graphed curve either recorded photographically or plotted from multiple observations. The first method gives little more information than that which was available to the old phlebotomists, and limits comparison of one test with another. The graphical record is in routine use in some laboratories and allows easy comparison of repeated tests on an individual, though comparison with tests on other persons is made rather difficult. Numerical records permit easier comparison and have been considered more practicable for this paper. A graphed curve of suspension stability usually records the crude S.S. In order to obtain the full benefit of the test performed in the method we have described, both the P.C.V. of the blood and the corrected S.S. of the one-hour reading should be recorded alongside the graph.

Summary

1. The practical method elaborated and now adopted in four British spa hospitals is as follows:

(*a*) Collect 8 to 10 c.c. venous blood oxalated with dry potassium oxalate to a concentration of 2 mgm. per 1 c.c. of blood.

(*b*) Fill to the 5 c.c. mark a 5 c.c. graduated (in 100 parts by volume) conical centrifuge tube. At the end of one hour read the volume of red-cell suspension still standing. This is the "crude S.S." (suspension stability). If a curve is desired, half-hourly readings may be taken over two hours.

(*c*) Fill a 100 by 5 mm. hæmatocrit tube and centrifuge this at 3,000 r.p.m. for fifteen minutes. Read off the packed red-

cell volume (P.C.V. per cent.). Alternatively, the P.C.V. may be obtained by centrifuging the 5 c.c. sedimentation tube after the sedimentation readings have been completed.

(*d*) The crude S.S. is viewed in the light of the presence or absence of anæmia, as shown by the P.C.V., and the S.S. is corrected to a standard P.C.V. of 42 per cent. by means of the following simple calculation:

If P.C.V. $<$ 42 per cent., add $1{\cdot}5 \times (42 - \text{P.C.V.})$ to crude S.S.

If P.C.V. $>$ 42 per cent., subtract $1{\cdot}0 \times (\text{P.C.V.} - 42)$ from crude S.S. (Correction Method II., p. 334.)

2. This correction method was chosen from four different mathematical methods propounded by the authors and statistically tested against corrections obtained by experimental manipulation of the cell-plasma volume ratio. It does not pretend to a high degree of mathematical accuracy, but it is designed as a simple device for the interpretation of the test in the light of variations in packed cell volume. Without assistance of this kind the mental adjustments necessary to assess the significance of fluctuations in S.S. when the cell volume percentage is also changing would be extremely difficult to make.

3. The standard P.C.V. at which corrected readings are given is 42 per cent. This is the mean of 400 unselected rheumatic cases of both sexes, and has been chosen as the standard figure for other reasons discussed in the text.

4. The sedimentation tube is of such dimensions that free fall of undiluted blood takes place, thus giving a true or natural reading and not one which is modified by the dilution of plasma by a citrate solution.

5. The hæmatocrit tube requires the use of a laboratory centrifuge, but possesses many advantages in addition to giving the P.C.V. upon which correction calculations may be based. Information concerning the red cells, the white cells, and the plasma may be gathered from it. It may also be used after filling but before centrifuging for a parallel sedimentation test, whereby the rare cases of inconsistent sedimentation may be detected.

6. The sedimentation test, as here described, is in the opinion of the authors the most accurate and informative method

where suitable conditions exist for its performance. In the absence of proper laboratory facilities, and in children where venous blood cannot be easily collected, its application may be limited.

7. Anomalies of sedimentation due to (*a*) inconsistent sedimentation, and (*b*) anæmia without diminished S.S., have been discussed in some detail and the manner in which such abnormalities may be detected has been described.

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AN INDEX OF THE SEDIMENTATION RATE ON A MATHEMATICAL BASIS

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From the Cheshire Joint Sanatorium

MANY observers maintain that in the Westergren method of determining the sedimentation rate (S.R.) of red blood cells (R.B.Cs.) on a column of blood 200 mm. high, the fall at the end of the first or second hour gives all the required information. In a method affected by many variable factors it is inadvisable to over-elaborate the technique; at the same time it is worth while to obtain the maximum of reliable information possible from the test. The first hour reading may give incomplete, and often misleading indication of the subsequent fall of the R.B.Cs. The second hour readings, though more constant than the first, may also fail to reveal subsequent variations in the S.R. It is useful and desirable where possible to record the fall of the R.B.Cs. over periods up to five hours when using the Westergren method.

In the following tables are given the sedimentation rates of bloods in which the first hour, second hour, or first two hours' readings are similar, but which show variations in subsequent observations. The figures represent millimetres per cent.

TABLE I.—FIRST HOUR SIMILAR.

First Hour.	*Second Hour.*	*Third Hour.*	*Fourth Hour.*	*Fifth Hour.*	*Index.*
1	3	4	6	8	(36)
1	16	23	26	28	(160)
5	9	12	16	20	(104)
5	33	39	42	44	(282)
15	27	33	35	36	(256)
15	34	41	47	50	(324)
25	36	42	45	48	(344)
25	43	52	58	60	(416)

TABLE II.—SECOND HOUR SIMILAR.

First Hour.	*Second Hour.*	*Third Hour.*	*Fourth Hour.*	*Fifth Hour.*	*Index.*
1	4	6	9	12	(52)
1	4	8	11	15	(63)
2	4	8	11	14	(64)
2	7	11	17	18	(92)
2	7	13	16	20	(96)
3	7	14	19	23	(109)
8	17	22	25	27	(171)
8	17	27	33	36	(206)
13	17	33	36	39	(237)

The method of recording such observations is next considered.

The plotting of a graph is probably the best way of recording multiple results, but is time-consuming, and while it is convenient to compare a few observations of the same case, it is almost impossible to compare large numbers of different cases.

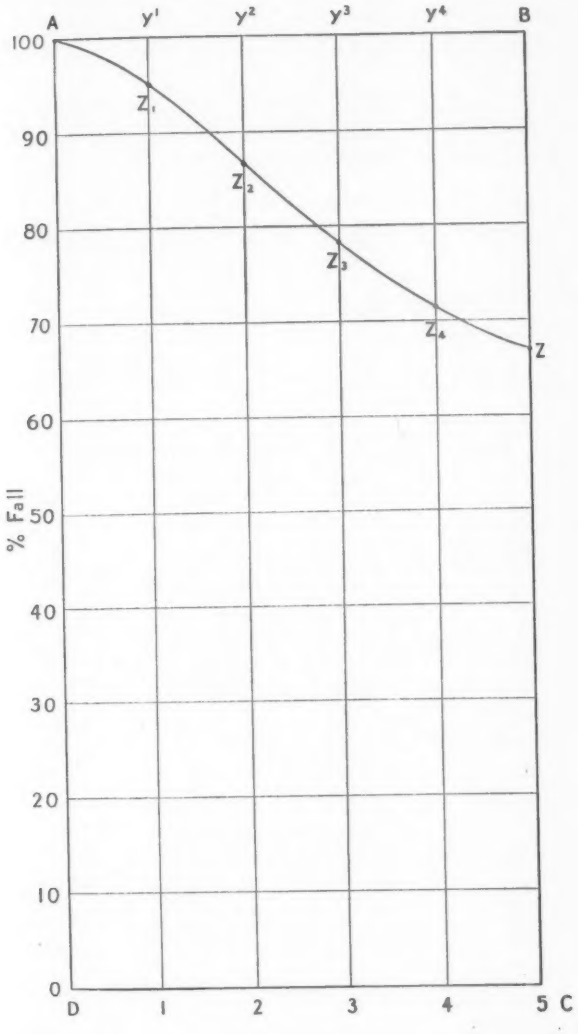
It is a great convenience if the S.R. can be expressed in a single number, provided that the number adequately reflects the variations in the S.R. at all readings. The recordings of the S.R. as a velocity expressed in mm. per minute is not always easy to determine, as the curve rarely shows a constant fall over any appreciable period of time. It also requires constant attention during the whole period of observation. Any number which is to represent effectively the S.R. must incorporate a relationship between the variables space (distance fall) and time. A graph reveals this two-dimensional relationship very well.

The figures in the brackets in Tables I. and II. under the heading "Index" are an attempt to incorporate in a single number the variations revealed at every observation of the sedimentation. The relationship, as mentioned above, is a two-dimensional one, and the index is the ratio of the area above the graph to the area of the rectangle formed by the ordinate (space) and abcissa (time), and expressed as the percentage, multiplied by 10, to obviate the use of the decimal point.

To simplify the calculation it is assumed that the fall between each reading is a straight line. This, of course, is not strictly correct, but as the curve is convex at one end and concave at the other they cancel out, and for all practical purposes the assumption is valid. The mathematical basis of the method is given below.

The area of ABZ, the portion of the rectangle ABCD above

the graph, is easily determined by adding together the area of the triangle AY_1Z_1 and the trapeziums $Y_1Y_2Z_2Z_1$, etc. This area, expressed as a percentage of the rectangle ABCD, is multi-



plied by 10 to obviate the decimal place. The calculation is made as follows:

SCALE IN CENTIMETRES AND MILLIMETRES.

The area of triangle AY_1Z_1

$= \frac{1}{2} \times AY_1 \times Y_1Z_1$
$= \frac{1}{2} \times 10 \times$ fall at end of 1st hour
$= 5 \times$ fall at end of 1st hour.

The area of trapezium $Y_1Y_2Z_2Z_1$

$$=\tfrac{1}{2}Y_1Y_2(Y_1Z_1+Y_2Z_2)$$
$$=\tfrac{1}{2}\times 10(Y_1Z_1+Y_2Z_2)$$
$$=5\times(\text{fall at end of 1st hour}+\text{fall at 2nd hour}).$$

The area of trapezium $Y_2Y_3Z_3Z_2$

$$=5\times\text{sum of fall at 2nd and 3rd hour, and so on.}$$

Total area of the portion above sedimentation graph is then: $5\times$[fall at 1st hour+(fall at 1st+2nd) . . . (fall at 4th+5th)] expressed as a percentage of the area of the rectangle ABCD, which is $50\times 100=5{,}000$ sq. mm.

$$=\frac{100\times 5\times[\text{fall at 1st hour}+(\text{fall at 1st}+2\text{nd})+\ldots(\text{fall 4th}+5\text{th})]}{5000},$$

and, as stated, the figure is expressed as per cent. $\times 10$; therefore the calculation is:

$$\frac{100\times 10\times 5\times[\text{fall at 1st}+(\text{fall at 1st}+2\text{nd})],\ \text{etc.}}{5000}$$

$$=\frac{5000\times[\text{fall at 1st}+(\text{fall at 1st}+2\text{nd})],\ \text{etc.}}{5000}$$

The 5,000 cancel, and we are left with

$$=\text{fall at 1st hour}+(\text{fall at 1st}+2\text{nd})+(\text{fall at 2nd}+3\text{rd})$$
$$+(\text{fall at 3rd}+4\text{th})+(\text{fall at 4th}+5\text{th}).$$

The actual calculation, which appears so complicated, is actually reduced to a very simple addition sum, as the following examples show:

Time.	*Fall (mm. per Cent.).*		
1 hour	1	Put down	1
2 hours	3	Add 1st and 2nd	4
3 hours	4	Add 2nd and 3rd	7
4 hours	6	Add 3rd and 4th	10
5 hours	8	Add 4th and 5th	14
			36

This index 36 is the percentage ($\times 10$) which the area ABZ is of the rectangle ABCD.

Index 36 = 3·6 per cent.

This example demonstrates the method. It will be seen, however, that each reading, except the fifth hour, occurs twice in the calculation. It can be further simplified by performing the calculation in the following ways:

Time.	*Fall (mm. per Cent.).*			
1 hour	1	Double	..	= 2
2 hours	3	Double	..	= 6
3 hours	4	Double	..	= 8
4 hours	6	Double	..	=12
5 hours	8	Add	..	= 8
				36

As the S.R. will have been measured in millimetres and the per cent. fall is the fall in millimetres divided by 2, it is only necessary to add together the first, second, third and fourth readings in millimetres and then add half the fifth reading. Thus:

Time.	*Fall (mm.).*				
First hour reading ..	2 ..	..	..	..	2
Second hour reading ..	6 ..	..	..	..	6
Third „ „ ..	8 ..	..	..	..	8
Fourth „ „ ..	12 ..	..	..	..	12
Fifth „ „ ..	16	half of 5th reading		..	8
					36

It will be seen that any variation in any reading will be reflected in the final index. The same mathematical treatment can be used to express in a single figure any series of multiple records which are at present best expressed by means of a graph.

These results are published by permission of Dr. Peter W. Edwards, Medical Superintendent; and to him and my colleague, Dr. Alan Lynn, my best thanks are due for their interest and suggestions.

Conclusions and Summary

1. The inadequacy of first or second, or both, hourly readings as a means of expressing the S.R. by the Westergren method is shown.

2. The disadvantages of the graphical representation are given.

3. An index is suggested and the mathematical basis of the index is indicated.

4. A suggestion made that the same method could be applied to any data which require graphical representation.

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REVIEWS

Environmental Factors in Rheumatoid Arthritis : a Study of the Relationship between the Onset and Exacerbations of Arthritis and the Emotional or Environmental Factors. Cobb, Bauer and Whiting. J.A.M.A., 1939, **113**, 668.

PRIOR to the advent of bacteriology as an established science and the many infectious theories concerning the ætiology of rheumatoid arthritis, much was written regarding the neurological theory by such workers as W. M. Ord, Kent Spender, A. E. Garrod, G. A. Bannatyne, H. W. Fuller, Dyce Duckworth, Osler and McCrae. Included in this theory were those who postulated the existence of lesions of the central nervous system, chiefly on account of the symmetrical joint involvement, as well as those who attributed the onset or exacerbation to some type of emotional shock, anxiety or worry. This latter view has more recently found considerable confirmation amongst workers both in America and England.

Specific cases have been recorded in which rheumatoid arthritis came on immediately after some emotional upset, where no other precipitating factor could be disclosed.* Such cases are probably within the experience of most workers in this field, and occurring as they do in a disease of unknown ætiology whose victims tend to suffer with vaso-motor, constitutional, gastro-intestinal and other symptoms of the type frequently encountered in the psychoneuroses, it seems curious that psychiatrists should for so long have neglected the investigation of this field of disease by their specialised methods.

The article under review describes a simple study planned to find out how often there was a relation in time—a synchronism of social factors and arthritic symptoms. For this study fifty patients with a typical rheumatoid arthritis were interviewed by a psychiatrist or a social worker, and the patient encouraged to talk in his own way about his life. In this way the main points were elicited, but no leading questions directly asked. The facts obtained were written on a life chart such as is used by Professor Adolf Meyer at the Johns Hopkins Hospital† and the medical data were subsequently added. This included all past illnesses as well as prodromal arthritic symptoms, onset of the arthritis, remissions and relapses, and the condition at the time of the interview.

In this way it can be found roughly how often the environmental burdens occurred at the time of the onset or an exacerbation of the arthritis. In some cases the patient himself emphasised this relationship in telling his own story. As the authors point out themselves, this method of study is not psychological in any deep sense, because

* Smith, Millard, *New Eng. Journ. Med.*, 1932, **206**, 211; Thomas, G. E., *Amer. Journ. Psychiat.*, 1936, **93**, 693.

† *Practical Clinical Psychiatry for Students and Practitioners.* P. Blakiston's Son and Co., Philadelphia, 1930.

the work was done too superficially to give anything more than an impression of the personality involved. It is, however, a study of considerable sociological importance which should certainly be amplified and followed up by other workers.

From a study of these life charts the author found that it seemed justifiable to divide the patients into three groups: (1) Those cases which appeared to have a close temporal relationship between the life stress and the arthritis: (2) those cases in which this relationship was doubtful; and (3) those cases in which no such relationship was evident. There was, in addition, a control group composed of patients entering the hospital for varicose ulcers who were investigated in exactly the same way, and whose age, sex and social status were similar. In only three of these twenty-five cases was there any coincidence of onset of ulceration and social stress.

In the first group in which such temporal relationship was observed definitely there were thirty-one patients—ten men and twenty-one women. Amongst the men a story of financial embarrassment was present in every case, whilst amongst the women the strain of nursing a sick relative was in addition a frequent finding.

The conclusions reached by these investigators were as follows: Environmental stress, especially poverty, grief and family worry, seem to bear more than a chance relationship to the onset and exacerbations of rheumatoid arthritis. The relative importance of these factors in the ætiology of rheumatoid arthritis can be established only by a much more detailed psychiatric study on a large group of such patients.

W. S. C. C.

Menopause Arthralgia. By Francis C. Hall, M.D. New England Journal of Medicine, vol. 219, 26, pp. 1015-1026.

This is a study of seventy-one women whose chief complaint was arthritis coming on after removal or destruction of the ovaries. In addition, the author has surveyed the extensive literature bearing on the subject and has discussed it in the light of a wide personal clinical experience. The result is a valuable monograph which deserves the close study of all who are interested in the problems of arthritis.

The incidence of rheumatic symptoms is far greater in women in the fourth and fifth decades than at any other epoch, and every type may be met with—fibrositis, infective, atrophic, and hypertrophic arthritis—but the problem is to define a form, the essential cause of which is endocrine disturbance associated with the menopause. That such a form exists is firmly believed by most writers on arthritis.

Rheumatoid arthritis of the ordinary type, polyarticular and atrophic, with a marked increase in the sedimentation rate, not infrequently has its onset at this age period, but is quite distinct from the form to which the author has given the name " menopause arthralgia," in which the sedimentation rate is usually normal or only slightly increased. The presence of a rapid sedimentation rate must always indicate the probability that the case is one of rheumatoid arthritis and not of the menopausal type. While in the later stages, if untreated, hypertrophic arthritis may result, a complete disappearance of symptoms occurs in many cases, and for this reason the author prefers

the designation arthralgia. The condition, which chiefly affects the knee-joints, though pains in other parts of the body are not uncommon, presents many affinities with fibrositis, and in the opinion of the reviewer should probably be placed in that category. Some of the cases present a raised blood uric acid which has been regarded as evidence of gout, but this idea, while suggestive, demands further proof. Many of the cases are overweight; this may be the cause of the pain in the back which is often complained of and is due to sacro-iliac strain.

The symptoms of the menopause are believed to be due to over-activity of the anterior pituitary flooding the body with the anterior pituitary sex hormones; coincidently there are symptoms of over-activity of the thyroid and the adrenal medulla, but on the other hand myxœdema may in some instances occur. It is suggested that these contrasting results may be associated with joint symptoms of different types, and some of the confusion which exists as to the exact nature of menopausal arthritis may be thus explained.

Dr. Hall has studied the effect of œstrogenic substance in the treatment of these menopausal complications with encouraging results. He stresses the need for adequate dosage and finds 10,000 to 100,000 international units are required weekly by the parenteral route for a period of about six weeks; by the oral route larger doses are necessary. He believes that the benefit is due to the introduction of a substance which inhibits the overactivity of the anterior pituitary. Beneficial results are not usually to be perceived until several doses have been given. In the author's series good results were experienced in 66 per cent. of the cases.

C. W. B.